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EATING OURSELVES TO DEATH AND DESPAIR: THE CONTRIBUTION OF ADIPOSITY AND INFLAMMATION TO DEPRESSION

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Abstract

Obesity and related metabolic conditions are of epidemic proportions in most of the world, affecting both adults and children. The accumulation of lipids in the body in the form of white adipose tissue in the abdomen is now known to activate innate immune mechanisms. Lipid accumulation causes adipocytes to directly secrete the cytokines interleukin (IL) 6 and tumor necrosis factor α (TNFα), but also monocyte chemoattractant protein 1 (MCP-1), which results in the accumulation of leukocytes in fat tissue. This sets up a chronic inflammatory state which is known to mediate the association between obesity and conditions such as cardiovascular disease, type 2 diabetes, and cancer. There is also a substantial literature linking inflammation with risk for depression. This includes the observations that: 1. People with inflammatory diseases such as multiple sclerosis, cardiovascular disease, and psoriasis have elevated rates of depression; 2. Many people administered inflammatory cytokines such as interferon α develop depression that is indistinguishable from depression in non-medically ill populations; 3. A significant proportion of depressed persons show upregulation of inflammatory factors such as IL-6, C-reactive protein, and TNFα; and 4) Inflammatory cytokines can interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity. While many factors may contribute to the association between inflammatory mediators and depression, we hypothesize that increased adiposity may be one causal pathway. Mediational analysis suggests a bi-directional association between adiposity and depression, with inflammation possibly playing an intermediary role.

Keywords

Obesity; inflammation; adiposity; depression; risk factors; cytokines; adipocytokines; fatty acids; lipids

1.0 Introduction

Obesity is of epidemic proportions in the U.S. and in many other parts of the world (Bornstein *et al*., 2008; Cumurcu *et al*., 2009; Wilborn *et al*., 2005). Not only are the rates of obesity and related metabolic conditions such as cardiovascular and liver disease, dyslipidemias, and type

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2 diabetes on the rise in adults; children and adolescents are also increasingly affected (Ben-Sefer *et al.*, 2009; MacPhee, 2008; Wang and Lobstein, 2006). In fact, more than 1 billion people are overweight worldwide, with more than 300 million meeting the definition of obesity (Shoelson *et al.*, 2007; World Health Organization, 2010).

In parallel with the rise in obesity has been an increase in associated endocrine (e.g., diabetes), metabolic (e.g., dyslipidemias), and other medical disorders (e.g., cardiovascular disease, hepatic steatosis [fatty liver disease], and certain forms of cancer) (Bellentani and Marino, 2009; Golden *et al.*, 2009; Hevener and Febbraio, 2010) as well as inflammation. For comprehensive reviews of the relationships between obesity, metabolic syndrome (MetS), and inflammation, see Shoelson (Shoelson *et al.*, 2007) Sutherland et al. (Sutherland *et al.*, 2004), and Dandona et al. (Dandona *et al.*, 2005). Emerging literature suggests that inflammation, as measured by elevated inflammatory cytokines and other inflammatory markers, may also represent both a cause and consequence of depression. As we will argue below, increasing evidence implicates obesity, high fat diets, and obesity-induced inflammation in the causal pathway for depression in some people. As well, evidence suggests that prior depression may increase risk for the subsequent development of adiposity. Therefore, depression and lipid accumulation in adipose tissue may form a mutually-enhancing dyad, in much the same way as body fat and other medical diseases. This paper will review the evidence for the association between adiposity and depression and will suggest that inflammation may serve as a possible causal link between these two common conditions.

2.0 Adiposity as a Risk Factor for Both Inflammation and Depression

2.1 Why Obesity? The Adaptive Value of Energy Retention in the Form of Lipids

Although modern constructs of obesity suggest that increasing body fat is “bad” from both a metabolic and cosmetic standpoint, the ability to absorb and retain high levels of energy stores has adaptive value (Wells, 2006). Fat deposition begins in the late gestational period and early infancy and contributes to infant fitness and survival (Kennaugh and Hay, Jr., 1987; Wells, 2006). Fat deposition increases again in adolescence and early adult life, particularly in females, which enhances the capacity to reproduce (Wells, 2006). Under conditions of unpredictable food sources, including the effects of seasons and periodic famines, fat deposition enhances the capacity to survive, reproduce and maintain survival of offspring (Wells, 2006). In particular, the capacity of humans to deposit large fat stores relative to many other species has been hypothesized to account, in part, for the ability to range well out of the typical temperate zones of primates (Wells, 2006). This ability to adapt to seasonal variations in energy availability has had extremely high adaptive value through most of human history. However, this general capacity for energy retention in the form of fat creates problems in the face of easy access to high calorie food. So, our ability to “forage and retain” calories appears to contribute to the propensity toward obesity in the human species. As noted by Wells (Wells, 2006), “the capacity to accumulate fat has therefore been a major adaptive feature of our species, but is now increasingly maladaptive in the modern environment where fluctuations in energy supply have been minimized, and productivity is dependent on mechanization rather than physical effort.”

2.2 Adipose Tissue

Body fat traditionally has been thought of as a simple depository of accumulated excess calories in the diet. However, fat in the form of adipose tissue is understood as a complex and multifaceted organ system (Mathieu *et al.*, 2009). There are two forms of adipose tissue in the body. The first is so-called brown adipose tissue (BAT)(also known as brown fat), which contains a large number of mitochondria and is highly metabolically active. A major purpose of BAT is to generate body heat (Enerback, 2009). Brown adipocytes have higher

concentrations of uncoupling protein 1 (UCP-1, also known as thermogenin) in the inner membrane of the mitochondria. UCPs alter the permeability of the inner mitochondrial membrane and allow proton leakage into the intermembranous space. Heat is generated by the uncoupling of the mitochondrial respiratory chain (Kozak *et al.*, 1988; Muzzin, 2002; Nicholls *et al.*, 1978). Brown adipose tissue is present in significant quantities in humans only in neonates (Fruhbeck, 2008; Vazquez-Vela *et al.*, 2008).

The second type of fat stored in the body is white adipose tissue (WAT) or white fat, which is the main site of long-term storage of fat in the body. WAT, particularly in the form of abdominal obesity, is the main contributor to diseases such as type 2 diabetes, cardiovascular disease, and certain forms of cancer associated with obesity (Calabro and Yeh, 2008; Despres *et al.*, 2008; Hevener and Febbraio, 2010). WAT serves several important roles in the body. The most obvious is the role of WAT as a storage site for triglyceride storage and release of fatty acids (Vazquez-Vela *et al.*, 2008). In this role, it breaks down complex triglycerides into glycerol and free fatty acids, which are used in energy metabolism. Adipocytes in WAT also secrete a variety of hormones, inflammatory factors such as cytokines (referred to as adipocytokines), and other proteins (Vazquez-Vela *et al.*, 2008) as described in greater detail below.

2.3 Lipids and Inflammation

2.3.1 Components of the Inflammatory Response—Inflammation is a complex and coordinated response of the body to a range of noxious stimuli. This can include infectious agents, such as bacteria or virus; however, the inflammatory response can also occur in response to other external or internal cues, including components of damaged or diseased tissues. For the purpose of the present discussion, inflammation is an immune response that largely derives from activation of the innate immune system. The innate immune response represents the initial and non-specific responsiveness of the body to infection, thereby providing immediate protection. Exposure to a pathogen (i.e., foreign protein) elicits a rapid, local cellular response, releasing a variety of factors including histamine, leukotrienes, prostaglandins, and chemokines (e.g., chemokine [CC-motif] ligands [CCL] 1–28). This response initiates the cardinal signs of inflammation, including redness and heat due to local vasodilation, edema, produced by extravasation of fluid from the vascular compartment, and pain. Chemokines (chemotactic cytokines) and related proteins function as chemoattractants for leukocytes (e.g., lymphocytes, monocytes). Local inflammation initially activates naïve T-lymphocytes, generating T-helper (CD4+) and cytotoxic (CD8+) cells (Harrington *et al.*, 2005; Stockinger *et al.*, 2007). Other leukocytes including macrophages are attracted to the site of local inflammation, leading to the release of inflammatory factors, particularly cytokines, which include interleukins (IL-1α, IL-1β, IL-2 – 35), interferons (IFNα, β, γ, and ω), and tumor necrosis factor (e.g., TNFα). Many of these cytokines are pro-inflammatory (e.g., IL-1α/β, IL-6), although some serve anti-inflammatory (e.g., IL-10, transforming growth factor-β [TGFβ]) and anti-apoptotic (e.g., IL-9) roles.

The generation of the initial inflammatory response depends on the recognition of specific pathogen-associated molecular patterns (PAMPs) associated with groups of microorganisms by a range of pattern recognition receptors. The prototypical gram-negative bacteria endotoxin protein is lipopolysaccharide (LPS). PAMPs, but also endogenous proteins from injured tissues activate - like receptors (TLRs), which are membrane-spanning pattern-recognition receptors (TLR1–TLR10 in humans) (Cook *et al.*, 2004). Activation of TLRs produces transductional activation of nuclear factor kappa B (NF-kB) as well as the mitogen-activated protein (MAP) kinase cascade including p38, JNK and ERK 1/2 pathways, resulting in an increased expression of cytokines (IL-1α and IL-1β), chemokines and other inflammatory mediators (Billack, 2006) (Hansson and Edfeldt, 2005)(Figure 1). IL-1 activation of IL-1 receptors induces the transcription of other proinflammatory (IL-6 and TNFα, which can also increase IL-1

expression) and anti-inflammatory (IL-10) cytokines. Activation of inflammatory signaling pathways also stimulates the synthesis of nitric oxide via specific nitric oxide synthases derived from endothelial cells (eNOS or NOS III), peripheral lymphocytes (inducible nitric oxide synthase [iNOS] or NOS II), and neuronal tissue (nNOS or NOS I) by activation of NADPH oxidase and NF-κB (Parul *et al.*, 2007; Wu *et al.*, 2008) (Wu *et al.*, 2008; Parul *et al.*, 2007). iNOS is induced by several cytokines including IFNγ and TNFα secreted in response to local inflammation. Nitric oxide (NO) serves a variety of functions, including vasodilation and neurotransmission; however, as a component of the immune system, NO is converted to S-nitrosothiols and related derivatives which function as free radicals that are toxic to invading organisms (Parul *et al.*, 2007; Hughes, 2008) (Figure 1). Of significance to the later discussion, oxidized ("minimally modified") low density lipoproteins (LDL) can also activate TLRs (specifically TLR4) leading to immune activation, including increased expression of the cytokines TNFα, MIP-2 (a mouse analogue to IL-8), and monocyte chemoattractant protein 1 (MCP-1; also known as cytokine (CC-motif) ligand 2 [CCL2]), a potent tissue chemotactic factor for activated monocytes/macrophages (Miller *et al.*, 2005c). Immune activation by LDL is an important mediating link between LDL and atherosclerosis (Hansson and Edfeldt, 2005). TLR3/4 activation also leads to cholesterol accumulation in cells via inhibition of the lipid-X receptor (LXR) – ABCA1 complex efflux mechanism (Hansson and Edfeldt, 2005).

Activation of the innate immune response eventually leads to the stimulation of T cells including T-helper cells which in turn contribute to the activation and maturation of B-cells. Mature B-cells including plasma B-cells, memory B-cells, B-1, B-2 subsequently respond with targeted phagocytosis and the generation of antibodies that target the pathogen in a specific manner (Montecino-Rodriguez and Dorshkind, 2006). This activation of acquired or adaptive immunity ultimately culminates in the ability to "remember" a prior exposure to a pathogen resulting in a more specific and rapid immune response to subsequent pathogen exposures.

Depending on the magnitude and/or extent of the inflammatory response, cytokines can enter the peripheral circulation and travel to the liver, inducing up- and down-regulation of a large number of acute phase reactants. Up-regulated proteins suppress microbe growth, increase coagulation, and both activate and suppress the inflammatory response. Key among these for the present discussion are the pentraxins; these include the so-called short pentraxin, C-reactive protein (CRP) and serum amyloid P-component (produced mainly by the liver) and the long pentraxin, pentraxin-3 (PTX3), produced by neuronal and other tissues (Livija *et al.*, 2009). PTX3 is a pattern-recognition protein, which is up-regulated by both cytokines and activation of TLRs. It has been shown to be up-regulated in peripheral tissues in people with depression without known inflammatory disease (Shelton *et al.*, 2003).

Dietary lipids, including polyunsaturated fatty acids (PUFAs) play significant roles in immune activation in the body. Fatty acids are long-chain esters of carboxylic acid, and exist in either saturated or unsaturated forms, depending on the presence or absence of double bonds in their structures. PUFAs contain multiple double bonds in their structures and are divided into n-3, -6, and -9 (also known as omega) fatty acids, depending on the position of the first double bond (IUPAC-IUB Commission on Biochemical Nomenclature, 1978). N-3 fatty acids are found in plants and fish and are the main constituents of fish oil used as a dietary supplement. PUFAs are incorporated into cell membranes and are metabolized into lipid signaling molecules and other compounds (Galli and Calder, 2009). Specific tissue types have particularly high concentrations of lipids, including brain and certain immune cells. PUFAs have complex roles in modulating immune responses. For example, arachidonic acid, a major n-6 fatty acid, is metabolized by cyclooxygenase (COX) enzymes to form eicosanoids and related compounds (e.g., thromboxanes and prostaglandins), which have predominantly pro-inflammatory effects (Rao and Knaus, 2008) (with the exception of anti-inflammatory lipoxins [Serhan, 2009[). By contrast, the major n-3 fatty acids such as eicosapentaenoic acid (EPA) and docsahexanoid

acid (DHA) give rise to specific anti-inflammatory molecules, including resolvins, protectins, and maresins (Galli and Calder, 2009; Serhan, 2009), which serve as cellular inflammatory stop signals. Early in the inflammatory process, inflammatory lipid derivatives such as the prostaglandins and leukotrienes predominate; however, with time, there is a shift to anti-inflammatory mechanisms. These mechanisms reduce the production of cytokines, block intracellular mechanisms involved in inflammatory signaling and leukocyte trafficking (Serhan, 2009). The anti-inflammatory benefits of aspirin have to do with the fact that it acetylates COX-2 and increases the synthesis of these anti-inflammatory mediators (Serhan *et al.*, 2002). For example, a lipidomic analysis of exudates obtained from mice treated with aspirin and DHA showed an increase in production of resolvins, which inhibit human microglial expression of cytokines in physiologically-relevant concentrations (Serhan *et al.*, 2002). These data suggest that the anti-inflammatory effects of aspirin, including its benefits in endothelial dysfunction in cardiovascular disease, may be mediated via these mechanisms.

2.3.2 White Adipose Tissue as an Endocrine Organ: Adipocytokines and Related Molecules—Adipocytes in WAT are far from inert storage cells. In fact, they produce a wide range of hormone and immune factors (Tilg and Moschen, 2008; Tilg and Moschen, 2006) (Figure 2). Important among these are the adipocytokines (adipokines), which are cytokines that are produced mainly by adipose tissue. These include resistin, and visfatin, but also IL-6 and TNFα, which are thought to link obesity and both inflammation in general and inflammatory disorders in particular (Tilg and Moschen, 2006). In fact, the increase in fat in adipocytes increases the production of chemokines, including MCP-1. MCP-1 attracts leukocytes including macrophages and other cell types including T lymphocytes, and dendritic cells to adipose tissue (Carr *et al.*, 1994; Xu *et al.*, 1996). Both adipose tissue itself and immune cells produce cytokines such as IL-1, IL-6, and TNFα, although macrophages are considered the primary source of inflammatory cytokines from adipose tissue (Tilg and Moschen, 2006). Indeed, WAT contains large numbers of macrophages, and activated macrophages also produce chemoattractant proteins, which lead to further accumulation of white blood cells and production of cytokines (Kanda *et al.*, 2006). Adipocytokines and related cytokine molecules produced by adipose tissue, particularly WAT, result in general immune activation by mechanisms noted earlier and, ultimately, can contribute to immune-related disorders (Tilg and Moschen, 2006). Obesity is generally associated with an increased inflammatory response, with excess production of adipocytokines, chemokines, cytokines, and acute phase proteins such as CRP, along with inhibition of protective molecules such as leptin and adiponectin, which contribute to common inflammatory diseases including type 2 diabetes and cardiovascular disease (Wellen and Hotamisligil, 2005). Interestingly, abdominal WAT (particularly intra-abdominal fat) produces a greater effect on systemic inflammation than other sites of WAT accumulation, possibly related to the relationship of intra-abdominal WAT to the portal circulation (Shoelson *et al.*, 2007). This is thought to occur, in part, as a result of cellular hypoxia that results from expansion of adipose tissue via compromised vasculature (Stuart, I *et al.*, 2009). The partial pressure of oxygen in most tissues is about 50 mmHg; lean WAT has been measured at 47.8 mmHg O_2, while WAT in obese mice was shown to be 15.2 (Trayhurn *et al.*, 2008; Ye *et al.*, 2007). Tissue hypoxia has been shown to be associated with many of the effects described in greater detail below, including increased expression of IL-1β, IL-6, and visfatin and reduced adiponectin (Stuart, I *et al.*, 2009). Intra-abdominal WAT can be particularly insidious since it may be increased in many people who are not overtly obese, and yet still contribute to inflammatory allostatic load. In fact, abdominal fat, not other measures of obesity such as body mass index (BMI), which simply reflects the ratio of weight in kilograms to height in meters squared, is much more predictive of diseases such as type 2 diabetes and cardiovascular disease (Shoelson *et al.*, 2007).

A variety of adipocytokines and related molecules that are produced by WAT are involved in the regulation of dietary intake, lipid distribution, and energy homeostasis (for a review, see

Frübeck (Fruhbeck, 2008) and Bays et al. (Bays *et al.*, 2008). For example, leptin, a member of the type I cytokine superfamily (Lago *et al.*, 2007; Lago *et al.*, 2009), is involved in the regulation of energy acquisition (eating) and expenditure in the body, acting primarily via the CNS (Vazquez-Vela *et al.*, 2008). Leptin receptors in the hypothalamus regulate satiety, the perception of dietary sufficiency. Leptin levels increase in obesity, which is related to loss of sensitivity to feedback regulation via leptin receptors (Considine*et al.*, 1996). It also has significant interactions with immune response, and is involved in the modulation of white blood cell response; this includes T-cell activation and a shift to Th1 cytokine production (Lago *et al.*, 2007; Lago *et al.*, 2009). Leptin also is increased by IL-1, IL-6, and LPS (Lago *et al.*, 2007). Therefore, although leptin is generally thought of as a protective factor regarding obesity, the elevated levels found in obese individuals may contribute to the inflammatory state.

Adiponectin is another peptide that is involved in a range of metabolic processes that are produced by WAT. For example, it increases fatty acid oxidation, reduces the synthesis of glucose in the liver and is involved in the feedback sensitivity of insulin receptors (Lago *et al.*, 2007; Lago *et al.*, 2009). Adiponectin levels are reduced in obese persons and increase in response to weight loss (Lago *et al.*, 2007). This mechanism, in part, explains the improvements in glucose metabolism associated with weight reduction, since adiponectin is protective against insulin resistance (Tilg and Moschen, 2006). Adiponectin has a predominantly inhibitory role in Th1 immune responses. For example, it inhibits macrophage IL-6 and TNFα production and increases systemic production of the anti-inflammatory cytokine IL-10 (Tilg and Moschen, 2006). This process occurs via activation of the two subtypes of adiponectin receptors, which activate the transcriptional factor peroxisomeproliferator-activated receptor-α (PPARα) (Tilg and Moschen, 2006). Alternatively, under certain states such as LPS activation adiponectin may have pro-inflammatory effects (Tilg and Moschen, 2006). Resistin is another adipocytokine that is produced by WAT but also is found in blood monocytes (Tilg and Moschen, 2006). It contributes to a positive inflammatory feedback system in which the secretion of resistin by adipose tissue is increased by IL-1, IL-6, and TNFα, but it also increases the production of these same cytokines by macrophages in a NF-κB – dependent manner (Silswal *et al.*, 2005; Tilg and Moschen, 2006). Resistin is thought to play an important role in obesity-induced insulin resistance and endothelial dysfunction leading to cardiovascular disease (Tilg and Moschen, 2008).

Adipose tissue also secretes anti-inflammatory cytokines including IL-10 and IL-1 receptor antagonist (IL-1Ra) (Juge-Aubry *et al.*, 2005; Juge-Aubry *et al.*, 2003). However, the role of these factors, particularly IL1Ra, is highly complex (Feve and Bastard, 2009). Increases in adipose tissue in humans, particularly abdominal fat, has been consistently shown to increase IL-1Ra expression (Fain, 2006; Somm *et al.*, 2006; Juge-Aubry *et al.*, 2003; Cartier *et al.*, 2009; Fain, 2006). Given its role in antagonizing IL-1 receptors, it would be expected to exert a simple anti-inflammatory action, which might have a positive effect in obesity-induced inflammation. In fact, in islet cells in the pancreas, IL-1Ra enhances insulin release and sensitivity and improves glycemic control via IL-1 blockade (Ehses *et al.*, 2009; Larsen *et al.*, 2009). However, IL-1Ra knockout mice have reduced fat mass, related to an increase in energy expenditure and a reduction in adipogenesis (Somm *et al.*, 2005). IL-1Ra alters extrapancreatic insulin sensitivity and glucose metabolism leading to a diabetes-type phenotype (Somm *et al.*, 2006). IL-1Ra null mice have increased insulin sensitivity and lower glucose levels in contrast to wild type (Somm *et al.*, 2006; Matsuki *et al.*, 2003). IL-1Ra is higher in older adults with MetS compared to non-affected controls (Stenholm *et al.*, 2009). IL-1Ra antagonizes the action of leptin in the hypothalamus in rodents and is thought to be involved in leptin resistance in obesity (Meier *et al.*, 2002). The ultimate role of IL-1Ra in weight regulation, leptin and insulin sensitivity remains controversial (Feve and Bastard, 2009). Of relevance to the current discussion, IL-1Ra has been assessed in clinically depressed

populations; the majority of studies have found it increased in depression, effects that were maintained even after adjusting for BMI (Howren *et al.*, 2009).

2.3.3 Metabolic Consequences of Lipid Accumulation: Obesity-Associated Inflammatory Diseases—A number of conditions that represent the major sources of morbidity and mortality in the modern world such as type 2 diabetes, cardiovascular disease, and cancer are known to be associated with obesity and have recently been reformulated as inflammatory diseases. For example, the inflammation associated with the accumulation of intra-abdominal fat is associated with progressive resistance to the effects of insulin, ultimately leading to type 2 diabetes. The chronic inflammatory state and changes in leptin, adiponectin, and resistin associated with obesity is thought to be associated with this process (Tilg and Moschen, 2008; Tilg and Moschen, 2006). In fact, obese individuals with type 2 diabetes have increase peripheral inflammatory factors including IL-6, TNFα, and CRP relative to obese individuals without diabetes (Tilg and Moschen, 2008; Tilg and Moschen, 2006). The mechanisms for obesity- and cytokine-induced insulin resistance appears to be, in part, related to mechanisms discussed for intracellular immune activation described earlier. Specifically, activation of JNK and IKKβ – NF-κB signaling cascades appear to be involved in the development of insulin resistance (Shoelson *et al.*, 2007; Tilg and Moschen, 2008; Tilg and Moschen, 2006). This occurs, in part, via the activation of pattern recognition receptors (e.g. TLRs) by fatty acids and, in particular, oxidized low density lipoproteins (also known as minimally modified LDLs [mmLDL]), which act primarily through TLR4 (Miller *et al.*, 2005b). TLR activation of JNK leads to phosphorylation of insulin receptor substrate-1 (IRS-1), a signal transduction factor associated with insulin receptors and insulin-like growth factor receptors, which disrupts insulin cellular signaling leading to insulin resistance. Dissociation of NF-κB from IKKβ leads to transcriptional activation of a variety of gene products that may also contribute to insulin resistance (Shoelson *et al.*, 2006).

A similar inflammatory process links obesity with cardiovascular disease. High LDL cholesterol and serum triglycerides have been thought in the past to lead to cardiovascular disease via simple deposition in small vessels. However, the process of atherosclerosis is now understood to be more complex and involve inflammatory factors leading to endothelial dysfunction in small vessels (Van Gaal *et al.*, 2006). For example, small dense LDL can transit via fenestrations in the endothelial lining of vessels and enter the subendothelial space, leading to a local inflammatory response. This, coupled with platelet aggregation and the activation of other pro-coagulation factors, leads to progressive occlusion of vessels, leading to a variety of conditions such as cardiovascular disease, peripheral artery disease, and, in men, erectile dysfunction (Van Gaal *et al.*, 2006). Obesity is often associated with a variety of factors such as smoking, increased levels of LDL cholesterol, abnormalities of glucose metabolism, and hypertension to increased risk of endothelial dysfunction leading to cardiovascular disease (Van Gaal *et al.*, 2006).

Although metabolic diseases like type 2 diabetes are commonly associated with obesity (that is, elevated total body mass), the contribution of diet to inflammatory diseases is more complex. For example, the phenomenon of so-called “normal weight obesity” (defined as a BMI <25 kg/m^2 and a percent body fat $\geq 66^{th}$ gender-specific percentile) is associated with signs of inflammation similar to that found in typical obesity (Marques-Vidal *et al.*, 2009; Stenholm *et al.*, 2009). A recent large study in Switzerland found normal weight obesity in 5.4% of women but <3% of men. Women with normal weight obesity had blood pressure, lipid levels, fasting hyperglycemia, CRP, and liver enzyme levels that were greater than that found in a lean sample and similar to an overweight group. These results indicate that body adiposity rather than weight or BMI may be the critical factor in inducing inflammation.

3.0 Inflammation and Depression

To this point we have discussed the inflammatory effects of lipid accumulation in adipose tissue. However, are adiposity and depression linked, and do the inflammatory effects of adipose tissue contribute to depression risk? In this section we will discuss the association between inflammation and depression, and then discuss specific linkages between fat accumulation and depression risk.

Pioneering work by Maes (Maes, 2008), Miller (Miller *et al.*, 2009), Irwin (Irwin and Miller, 2007b), and many others over the last 20 years has demonstrated that a significant subset of depressed patients show evidence of innate immune system activation. Some of the very earliest findings, dating to the late 1980's, suggested alterations in circulating levels of specific subtypes of lymphocytes such as T-helper and natural killer cells; however, these results were not consistently replicated (Irwin and Miller, 2007a). However, subsequent research has shown that a sizeable subset of depressed patients have evidence of activation of innate immunity in the absence of obvious underlying medical causes (Miller *et al.*, 2009). These include the pro-inflammatory cytokines and their soluble receptors in peripheral blood and cerebrospinal fluid (CSF), along with increased acute phase proteins (e.g., CRP), chemokines, cell adhesion molecules, and other inflammatory mediators such as prostaglandins (Levine *et al.*, 1999a; Miller *et al.*, 2009; Raison *et al.*, 2006). The most consistently replicated findings include elevations of serum IL-6, TNFα, and CRP (Raison *et al.*, 2006; Miller *et al.*, 2009; Dowlati *et al.*, 2010; Howren *et al.*, 2009). A number of studies have also shown higher IL-1β (Kaestner *et al.*, 2005; Levine *et al.*, 1999b; Schlatter *et al.*, 2004; Thomas *et al.*, 2005; Yang *et al.*, 2007), although this has been less consistently replicated. Elevations in inflammatory mediators are seen across the life span, including elderly depressed patients both with and without co-existing medical diseases (Andrei *et al.*, 2007; Tiemeier *et al.*, 2003).

3.1 Sickness Behavior: Animal and Human Models of Depression

So-called "sickness behavior" represents an adaptive response of animals seen during the course of an infection (Hart, 1988; Weidenfeld and Yirmiya, 1996; Pollak and Yirmiya, 2002; Dantzer *et al.*, 2008; Dantzer, 2009) (Figure 3). In humans, sickness behavior comprises fever, malaise, fatigue, muscle and joint aches, and reduced appetite (Dantzer *et al.*, 2008; Dantzer, 2009). However, peripheral immune activation in both humans and other vertebrates can induce sickness symptoms that show considerable overlap with depression, including depressed mood, reduced social interaction, and sleep disturbance (as discussed in greater detail below) (Capuron *et al.*, 2009). Hence, inflammatory-induced sickness behaviors include a number of features that are consonant with the human syndrome of major depression.

The molecular mechanisms underlying this response involve innate immune activation, including IL-1α, IL-1β, IL-6, and TNFα (Dantzer *et al.*, 2008; Dantzer and Kelley, 2007a). These induced cytokines, then, set up the local immune response to the invading pathogen. Although the initial immune activation may be primarily peripheral, as in the case of infection, these peripheral immune responses can access and ultimately influence the brain. Because cytokines are too large to freely pass through the blood brain barrier, much attention has been paid to how cytokine signals access the brain; several pathways have been described (Figure 3). For example, local release of cytokines can activate afferent neurons (including the vagus nerve) innervating the infected tissues; these afferent neurons, in turn, lead to activation of microglia resulting in brain production of cytokines. A second route is a humoral pathway by which cytokines can activate leukocytes in the choroid plexus and circumventricular organs, setting up a local immune response, resulting in diffusion of cytokines into brain through leaky regions in the blood brain barrier (Dantzer, 2009). The circumventricular regions include the organum vasculosum of the lamina terminalis, the subfornical organ, the median eminence and the area postrema. These areas have a rich vasculature in which the capillary endothelial cells

lack tight gap junctions, which allows the diffusion of large molecules such as the cytokines (Nguyen *et al.*, 2002). Of note, peripheral cytokines can also cross the blood brain barrier via saturable active transport molecules (Quan and Banks, 2007). Regional CNS cytokines stimulate endothelial cells in small blood vessels to release prostaglandin E2 (PGE2) and nitric oxide (NO), which appear to be important mediators of the brain-based symptoms of the immune response such as fatigue and lethargy (Dantzer, 2009).

An additional pathway by which peripheral inflammation can be communicated to the brain includes the release of MCP-1 by activated microglia. MCP-1 recruits peripherally activated monocytes which can directly enter the brain and subserve central inflammatory responses (D'Mello *et al.*, 2009). As noted previously, this role of MCP-1 in attracting activated macrophages to relevant tissues also appears to be important to the accumulation of macrophages in adipose tissue as well as areas of vascular injury (e.g. atherosclerotic plaques) (see below). In rodents, cytokine activation of sickness behavior has been shown to be mediated by IL-1β (Anforth *et al.*, 1998); however, this response appears to be augmented by co-expression of IL-6 (Bluthe *et al.*, 2000b) and TNFα (Bluthe *et al.*, 2000a). Inflammatory mediators also stimulate the preoptic nuclei of the hypothalamus to induce fever (Romanovsky *et al.*, 2005). Therefore, peripheral immune activation acts indirectly to set up a brain inflammatory response. As will be discussed in greater detail later, antagonism of peripheral mediators of inflammation may also reduce the central inflammatory response and related behavioral features (Krishnan *et al.*, 2007; Tyring *et al.*, 2006a).

Cytokines, primarily IL-1β, also stimulate the release of corticotrophin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus (Figure 3). CRH stimulates the release of adrenocorticotrophic hormone (ACTH) from the pituitary, which travels via the systemic circulation to the adrenals where it induces the release of cortisol. Cortisol inhibits and, therefore, limits the local inflammatory response, both peripherally and centrally. This occurs, in part, by inhibition of IL-1, and other inflammatory cytokines such as TNFα and IL-6 (DeRijk *et al.*, 1997). Curiously, however, whereas TNFα is very sensitive to cortisol-induced downregulation, IL-6 is relatively resistant at typical physiological levels (DeRijk *et al.*, 1997). This is significant since elevated IL-6 has been a consistent finding in studies in depressed patients, despite concomitant elevation of cortisol (Irwin and Miller, 2007a).

Sickness behavior has been consistently shown with immune activation in non-human vertebrates (Dantzer, 2009; Dantzer and Kelley, 2007). One striking example comes from a study of infusion of IFNα in non-human primates (Felger *et al.*, 2007). In this study, Felger and colleagues (Felger *et al.*, 2007) administered recombinant human IFNα or saline to rhesus monkeys in a counterbalanced fashion over 4 weeks. IFNα infusion was associated with increased anxiety-like behaviors and decreased environmental exploration; in a subset of monkeys, IFNα administration was also linked to huddling behavior, a behavior also observed after chronic administration of the monoamine depleting drug, reserpine, as well CRH. IFNα infusion was associated with elevations in plasma IL-6, ACTH, and cortisol, which diminished over time. Curiously, the time-dependent decreases in ACTH, cortisol, and IL-6 were more pronounced in socially dominant than in submissive animals. Similar results have been found in humans, as discussed below (Capuron *et al.*, 2003b)

3.1.1 Sickness Behavior in Humans—Immune activation in humans shows a pattern of symptoms consistent with sickness behavior in animal models. Symptoms such as fatigue, malaise, anorexia, and sleep disturbance are common in the context of immune activation (Dantzer and Kelley, 2007); this can be seen as part of the core symptoms in certain diseases such as rheumatoid arthritis, but also as part of the response to treatments. For example, cancer chemotherapy agents such as paclitaxel induce immune responses (e.g., IL-6, IL-8, and IL-10), which correlate with symptoms such as fatigue (Pusztai *et al.*, 2004). However, is sickness

behavior really analogous to depression? The question about the relationship between sickness behavior induced by immune activation and human depression was addressed recently by Capuron et al. (Capuron *et al.*, 2009) Administration of immune factors such as IFNα and IFNβ, TNFα, IL-1, and IL6 as well as immune activators such as LPS had previously been shown to induce depressive-like signs and symptoms (Capuron *et al.*, 2002a; Capuron *et al.*, 2009; Capuron and Miller, 2004; Matrisciano *et al.*, 2009). In this study, 20 persons who were being treated with INFα for malignant melanoma were compared with 28 medically healthy persons with major depression. All participants were evaluated with the Structured Clinical Interview for DSM Axis I Disorders (First *et al.*, 2002) and the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). IFNα-treated participants could not have a current diagnosis of major depression or substance-related disorder at baseline; none had a history of any anxiety disorder and only 5 of 20 IFNα-treated patients had a history of depression. The IFNα-treated patients were followed weekly for 12 weeks. Nine of the 20 (45%) IFNα-treated patients developed depressive signs and symptoms sufficient to meet criteria for major depression. Comparing the depressed IFNα-treated patients and the medically-healthy depressed patients, there were no mean differences in the HRSD total score (21.3 vs. 20.4 respectively) or in the severity of the following HRSD items: depressed mood, psychic anxiety, hypochondriasis, agitation, somatic anxiety, and impairment of work and activities. IFNα-treated patients showed more psychomotor retardation and weight loss than the medically-healthy depressed sample. The latter exceeded the IFNα sample in only two categories: feelings of guilt and thoughts of suicide (Capuron *et al.*, 2009). These results indicate that the depression induced by immune challenge emulates, and in the case of some features exceeds, that seen in depression in medically-healthy persons. Also consistent with this view are observations that aspects of sickness behavior can be reversed or prevented by the use of antidepressant treatments (as discussed further below) (Musselman *et al.*, 2001; Yirmiya *et al.*, 2001; Capuron *et al.*, 2002; Raison *et al.*, 2007)

3.2 Associations Between Inflammatory Mediators and Depression in Medically Ill Persons

Patients with a variety of inflammatory diseases, including certain forms of cancer (Musselman *et al.*, 2001b), rheumatoid arthritis (Zautra *et al.*, 2004), and multiple sclerosis (Gold and Irwin, 2006), have been shown to have increased rates of depression. Depression in these patients also appears to be associated with increased inflammatory cytokine levels. For example, several studies have shown that depressed cancer patients show higher levels of IL-6 than either normal controls or non-depressed cancer patients. (Jehn *et al.*, 2006; Lutgendorf *et al.*, 2008; Musselman *et al.*, 2001b; Soygur *et al.*, 2007) The severity of depression in some cancer patients has also been shown to be correlated with IL-6 levels; for example, Jacobson et al. (Jacobson *et al.*, 2008) found a high degree of correlation between IL-6 level and depression as measured by the HRSD (r=0.68) in cancer patients. The same association between pro-inflammatory factors, including both IL-6 and CRP, and depression has been shown for patients with cardiovascular disease (Miller *et al.*, 2005a). Of significance for the discussion of the relationship between adiposity and depression risk below, this same study showed an association between body mass and depression, which partially accounted for the correlation between CRP and IL-6 and depression. Depressed subjects had a significantly greater mean BMI (BMI=30.5) compared to controls (BMI=25.9) and BMI was positively related to levels of CRP (r = 0.62) and IL-6 (r = 0.63). This is consistent with the hypothesis articulated below that there may be a link between body adiposity, inflammation, and depression risk. In general, pro-inflammatory cytokines may mediate the relationship between many diseases and depression risk.

3.3 Mechanisms by Which Immune Activation Leads to Depression

3.3.1 Activation of Indoleamine 2,3-dioxygenase: Effects on Serotonin and Kynurenines—Depression has been linked to the function of monoamines (serotonin,

norepinephrine, and dopamine) for decades, owing in large part to the fact that effective antidepressant drugs consistently target these transmitters (Maas, 1975; Maas, 1978; Schildkraut, 1995). Depletion of monoamines (serotonin and norepinephrine) has been shown to induce depressive signs and symptoms in some drug-free patients (Delgado *et al.*, 1994) and to rapidly reverse the effects of antidepressants leading to depressive relapse (Delgado *et al.*, 1990; Delgado *et al.*, 1991; Delgado *et al.*, 1993; Delgado *et al.*, 1999).

Cytokine signaling has been shown to profoundly influence central monoamine synthesis, metabolism, and cellular transit, particularly that of serotonin. Serotonin is synthesized from tryptophan by tryptophan hydroxylase (TH) and aromatic amino acid decarboxylase (AAAD) (Figure 4). The amount of serotonin synthesized in brain is highly dependent on tryptophan availability (Delgado *et al.*, 1990). Depletion of tryptophan rapidly leads to reduced central serotonin levels (Delgado *et al.*, 1990). Under normal physiological conditions, the idoleamine 2,3-dioxygenase (IDO) (and the related liver enzyme tryptophan 2,3-dioxygenase) pathway competes with tryptophan metabolism by TH. Activation of the IDO pathway metabolizes tryptophan to kynurenine and, ultimately, to quinolinic acid (QUIN) (among other byproducts) (Stone and Darlington, 2002). This is thought to deplete brain tryptophan and reduce the amount of serotonin (Schrocksnadel *et al.*, 2006;Schwarcz and Pellicciari, 2002).

Multiple inflammatory signaling pathways activate IDO, particularly those associated with TNFα (Popov *et al.*, 2006) and IFNγ. (Takikawa *et al.*, 1999). These include signal transducer and activator of transcription 1a (STAT1a), interferon regulatory factor-1 (IRF1), NF-κB, and p38 mitogen activated protein kinase (p38 MAPK) (Miller *et al.*, 2009). Peripheral administration of LPS in mice has been shown to activate IDO and cause depressive-like behavior, including increased duration of immobility in the forced-swim and tail suspension tests (O'Connor *et al.*, 2009). Inhibition of inflammation-induced IDO induction by the tetracycline antibiotic minocycline or direct IDO inhibition by the IDO antagonist, 1-methyltryptophan, prevents depression-like behaviors in LPS-treated mice. These results indicate that the activation of IDO contributes to the depressogenic effects of immune activation (O'Connor *et al.*, 2009).

The effect of immune activation on tryptophan availability and kynurenine synthesis has also been tested in humans. In one study (Capuron *et al.*, 2002b), cancer patients undergoing treatment with either IL-2 or IFNα experienced reduced serum tryptophan at one week and one month of therapy compared to baseline. Depressive symptoms were positively correlated with the degree of decrease in tryptophan concentrations during treatment. In a second (Capuron *et al.*, 2003a), patients with malignant melanoma were given IFNα therapy; plasma kynurenine and the kynurenine/tryptophan ratio increased in all patients. Those patients who developed depression had higher kynurenine and lower tryptophan levels than those without depression. Patients receiving IFNα therapy show increases in IFNα, IL-6 and MCP-1 and decreases in the primary metabolite of serotonin 5-hydroxy indoleacetic acid (5-HIAA) in CSF; 5-HIAA levels had the strongest association with depressive signs and symptoms (Raison *et al.*, 2009a). In that study, CSF IL-6 but not IFNα or MCP-1 concentrations correlated significantly with 5-HIAA level. These results indicate that the development of depressive symptoms in patients undergoing cytokine therapy could be mediated by a reduced availability of tryptophan and, ultimately, serotonin in brain by activation of IDO.

When serotonin is released from presynaptic terminals, the signal is rapidly inactivated through reuptake via the high-affinity serotonin transporter (5HTT) (Blakely and Berson, 1992). Many antidepressant drugs block this transporter and lead to sustained synaptic serotonin signaling. Activation of p38 MAPK by both IL-1β and TNFα has been shown to lead to phosphorylation of the 5HTT and increased uptake of serotonin (Figure 4)(Zhu *et al.*, 2005). 5HTT trafficking to the cell surface has also been shown to be dependent on the activity of p38 MAPK (Samuvel

et al., 2005). In a related study, IFNα was shown to increase MAPK phosphorylation and both the expression and activity of 5HTTs in an immortalized line of T lymphocytes, effects that were reversed with a MAPK-selective inhibitor (Tsao *et al.*, 2008). Similar results were also shown in leukocytes obtained from depressed patients compared with controls (Tsao *et al.*, 2006). In this study blood samples were obtained from 20 drug-free persons with depression and 22 controls and leukocytes were extracted at baseline and after treatment with fluoxetine. At baseline, mRNA expression of IL1β, IL-6, IFNγ, TNFα, and the 5HTT were higher in the depressed patients than controls. The mRNA expressions of IFNγ and the 5HTT diminished after fluoxetine treatment. Taken together, these studies suggest that cytokines may reduce serotonin signaling via at least two mechanisms: metabolism of tryptophan to kynurenine by activation of IDO and p38 MAPK – dependent increase in expression and phosphorylation of 5HTTs resulting in increased synaptic uptake of serotonin.

The relevance of the effects of immune activation on serotonin to depression is also supported by studies that have examined the effects of serotonergic antidepressants in patients treated with IFN and other immunotherapeutics. In one study (Musselman *et al.*, 2001a), 40 patients treated with malignant melanoma treated with IFNα-2b were randomly assigned to concomitant treatment with the serotonin reuptake inhibitor paroxetine or placebo for 12 weeks. Only 11% of the paroxetine-treated patients developed depression as opposed to 45% of the placebo group. A reanalysis of the data from this study found that symptoms of depression such as depressed mood, anxiety, cognitive dysfunction, and pain were improved with paroxetine, while fatigue and anorexia were not helped (Capuron *et al.*, 2002a). The beneficial effects of serotonin reuptake inhibitors on depressive symptoms induced by immunotherapy (e.g., IFN treatment) has been supported by most ((Capuron *et al.*, 2002)Gleason *et al.*, 2007; Hauser *et al.*, 2002; Kraus *et al.*, 2008; Laguno *et al.*, 2004; Levenson and Fallon, 1993; Loftis *et al.*, 2004; Morasco *et al.*, 2007; Raison *et al.*, 2007; Sammut *et al.*, 2002; Schaefer *et al.*, 2005; Schramm *et al.*, 2000) but not all (Morasco *et al.*, 2007) studies. However, the overwhelming evidence suggests that concomitant treatment with serotonin reuptake inhibitors can either reverse or prevent immunotherapy-induced depressive symptoms.

In addition to its potential effects on tryptophan and serotonin availability, IDO activation yields several neuroactive intermediates that may also be involved in depression. For example, kynurenine is metabolized by kynurenine hydroxylase to kynurenic acid (KYN-A), which antagonizes α7 nicotinic acetylcholine receptors (Figure 4) (Schwarcz and Pellicciari, 2002). α7 receptor blockade leads to reduced striatal dopamine release (Amori *et al.*, 2009;Rassoulpour *et al.*, 2005), which is also seen in the brains of depressed persons (Dunlop and Nemeroff, 2007). A second byproduct of IDO activity is QUIN, which is produced by activation of kynurenine 3-monooxygenase (KMO). In addition to contributing to lipid peroxidation, QUIN is a potent activator of N-methyl-D-aspartic acid (NMDA) receptors and the release of glutamate, all of which can lead to excitotoxicity. (Jang *et al.*, 2010) This mechanism has been implicated in the pathophysiology of conditions such as Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, and human immunodeficiency virus-related dementia (Brew *et al.*, 2007;Guillemin *et al.*, 2005;Kwidzinski and Bechmann, 2007;Mosley *et al.*, 2006;Owe-Young *et al.*, 2008;Sas *et al.*, 2007;Vamos *et al.*, 2009;Zadori *et al.*, 2009). Therefore, IDO activation may contribute to the pathophysiology of depression by several mechanisms, including depletion of tryptophan and serotonin, reduced striatal release of dopamine, and NMDA receptor-glutamate-dependent excitotoxicity. It should be noted that KYN-A reduces glutamate release, which might be expected to antagonize the excitotoxic effects of QUIN via NMDA receptors. However, immune activation increases kynurenine 3-monooxygenase activity, shifting the metabolism of kynurenine away from KYN-A and toward QUIN (Connor *et al.*, 2008).

The administration of IFNα therapy has been shown to significantly shift the ratios of kynurenine and both tryptophan and kynurenine metabolites in humans. In one study, 16 patients with chronic hepatitis C without depression at baseline were treated with IFNα and showed increases in depression scores and the kynurenine to tryptophan ratio, consistent with enhanced IDO activation (Wichers *et al.*, 2005). The kynurenine to KYN-A ratio also increased, and the changes in the measure of depression severity correlated with the change in the ratio. This was taken to indicate that IFNα infusion resulted in not only IDO activation but also a diversion from KYN-A, which is relatively neuroprotective, to neurotoxic metabolites of kynurenine such as QUIN.

A recent study supports the concept of a shift from tryptophan to both kynurenine and neuroactive metabolites by exogenous immunotherapy. Raison et al. (Raison *et al.*, 2009b) conducted a study in which they measured tryptophan, kynurenine, KYN-A, QUIN, cytokines, chemokines, and soluble cytokine receptors in the CSF and blood of 27 patients with hepatitis C; 16 of whom were receiving IFNα treatment and 11 of whom were not. The immunotherapy markedly increased both blood and CSF kynurenine; CSF kynurenine was associated with a significant increase in both KYN-A and QUIN, but did not change CSF tryptophan concentrations in spite of reduced plasma tryptophan levels. Kynurenine and QUIN levels were correlated with depressive signs and symptoms and CSF IFNα, soluble TNF receptor 2, and MCP-1 (CCL2). These data strongly indicate that IFNα infusion resulted in activation of IDO resulting in increases in both kynurenine and the putative neurotoxin QUIN, and that these changes were associated with increases in depressive symptoms.

As with the role of pro-inflammatory cytokines in general discussed earlier, activation of inflammatory factors related to obesity also appears to induce the IDO – kynurenine pathway. For example, plasma tryptophan concentrations have been shown to be reduced in obese individuals (Breum *et al.*, 2003). Specifically, obese persons have a significantly higher kynurenine to tryptophan ratio relative to lean controls, signifying IDO activation (Brandacher *et al*., 2006; Breum *et al*., 2003). Nevertheless, significant weight reduction via change in diet (Breum *et al.*, 2003) or bariatric surgery (Brandacher *et al.*, 2006) has not been shown to restore tryptophan balance. This in part may be related to a relative lack of change in inflammatory factors after rapid weight loss (Brandacher *et al.*, 2006), although more delayed responses may be seen (Tziomalos *et al.*, 2010). Therefore, the immune activation found in obesity may contribute to the same diversion of tryptophan metabolism from serotonin to kynurenine, which could contribute to depression.

3.3.2 Effects of Immune Activation on Dopamine Dynamics—Reduced prefrontal and straital dopamine activity is thought to underlie symptoms of depression such as diminished motivation, psychomotor slowing, fatigue, and lack of response to rewarding stimuli (anhedonia) (Dunlop and Nemeroff, 2007; Salamone and Correa, 2009) Patients undergoing immunotherapy commonly experience fatigue and lethargy even if they do not experience a full major depressive episode (Capuron *et al.*, 2002a; Capuron *et al.*, 2009; Dantzer and Kelley, 2007). IFNα therapy has also been shown to produce significant motor slowing on neuropsychological assessment, which correlated with symptoms of fatigue and depression (Majer *et al.*, 2008). Positron emission tomography imaging studies in humans undergoing IFNα therapy show increased striatal resting state glucose metabolism (Capuron *et al.*, 2007; Juengling *et al.*, 2000). This is similar to Parkinson's disease, a condition associated with reduced striatal dopamine and increased striatal resting state metabolic activity (Spetsieris *et al.*, 2005). Infusion of the dopamine precursor levodopa reduces striatal activity, which is associated with improvements in motor signs in Parkinson's patients (Feigin *et al.*, 2001). Treatment with pro-dopaminergic agents such as levodopa or psychostimulants improve fatigue symptoms in patients with Parkinson's disease, cancer, systemic HIV, and those undergoing IFNα therapy (Breitbart *et al.*, 2001; Lou *et al.*, 2003; Schwartz *et al.*, 2002).

There is also evidence from animal studies implicating reduced dopamine turnover with immune activation. For example, IFNα administration in rhesus monkeys has been associated with reduced CSF level of a metabolite of dopamine, homovanillic acid, suggesting reduced turnover of dopamine. This was also associated with huddling behavior, considered a behavioral analogue of human anxiety and depression (Felger *et al.*, 2007). Similarly, whole brain homogenates from mice given species-specific IFNα for five days showed significantly reduced dopamine and its metabolite, 3,4-dihydroxyphenylacetic acid, which was associated with motor slowing (Shuto *et al.*, 1997). Together, these data suggest that immune activation, particularly exogenous administration of IFNα, is associated with reduced dopamine neurotramission, and may account for abnormalities in dopamine activity in depression (Miller, 2009).

Given the shift from KYN-A to QUIN synthesis, the α7 receptor blockade by KYN-A may not be a sufficient explanation for the hypodopaminergic state associated with depression. However, there are alternative mechanisms by which immune activation may alter dopamine transmission. For example, peripheral administration of IFNα to rats reduced brain concentrations of tetrahydrobiopterin (BH4), a co-factor for tyrosine hydroxylase, the rate limiting enzyme in dopamine, epinephrine, and norepinephrine synthesis from tyrosine (Kitagami *et al.*, 2003). The relationship between interferons and BH4 is complex. BH4 synthesis is increased by interferons (Gilchrist *et al.*, 2003; Shi *et al.*, 2004; Fujiwara *et al.*, 2004; Amri *et al.*, 2007). However, BH4, which is a cofactor for NOS-dependent synthesis of NO, has also been shown to be degraded following IFNα stimulation of NO synthesis, leading to reduced catecholamine synthesis (Kitagami *et al.*, 2003). This effect was reversed by the NO synthase inhibitor N^G-monomethyl L-arginine (Kitagami *et al.*, 2003). A similar effect on BH4 degradation and catecholamine synthesis has been reported in sympathetic neurons following peripheral administration of IL-6 (Li *et al.*, 2003).

Another mechanism that may alter brain dopamine dynamics is the effect of immune activation on the dopamine transporter (DAT). DAT is the principal mechanism for terminating dopamine synaptic signaling. Phosphorylation of DAT by MAPK kinase (MEK) regulates trafficking of DAT, increasing DAT surface expression and uptake of dopamine in a MAPK dependent manner in both rat synaptosomal and human embryonic kidney (HEK) cell lines (Moron *et al.*, 2003). The co-administration of MAPK inhibitors was shown to decrease DA uptake. Together, these studies suggest that immune activation in the CNS may also alter dopamine dynamics, which may contribute to some of the cardinal symptoms of both sickness behavior and depression, such as low energy, reduced motivation, and decreased responsiveness to rewarding stimuli.

3.3.3 Immune Activation and the Regulation of the Hypothalamic-Pituitary-Adrenal Axis—Overactivation and impaired feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis are some of the most consistently replicated findings in patients with depression (Gillespie and Nemeroff, 2005; Gold and Chrousos, 2002; Pace *et al.*, 2007a; Plotsky *et al.*, 1998). A variety of factors, particularly stress, increase the release of CRH and arginine vasopressin (AVP) from the paraventricular nucleus (PVN) of the hypothalamus (Lolait *et al.*, 2007). CRH and AVP subsequently stimulate the release of adrenocorticotropic hormone (ACTH) from the pituitary, which travels via the peripheral circulation to the adrenals and enhances the secretion of cortisol. Cortisol functions as a feedback regulator of the HPA axis, acting via glucocorticoid receptors (GR) in the hypothalamus, pituitary, and other brain regions. A significant subset of depressed persons show: 1. Elevations in the 24-hour excretion of cortisol in the urine; 2. Elevations in plasma cortisol and adrenocorticotropic hormone (ACTH); 3. Elevations in CSF levels of CRH; 4. Failure of feedback inhibition of cortisol secretion by the cortisol analog dexamethasone; and 5. A blunted ACTH but normal cortisol secretion to exogenously administered corticotrophin

releasing hormone (CRH) (Gillespie and Nemeroff, 2005). These results are taken as evidence of reduced availability of receptors for CRH and cortisol. Reduced GRs are thought to mediate the failure of feedback inhibition of secretion of cortisol on HPA axis activity (Gillespie and Nemeroff, 2005).

As noted earlier, cytokines, primarily IL-1β, stimulate the release of CRH from the hypothalamic PVN (Miller *et al.*, 2009). A single administration of exogenous IL-1 has been shown to produce sustained increases in expression of CRH, the CRH receptor CRH-R1, and AVP for up to three weeks in rats (Schmidt *et al.*, 2003). Some research has indicated that the CRH and AVP response to specific types of immune challenges may be different. In one study, peripheral administration of an adjuvant (*mycobacterium butyricum*) that induced arthritis in rats resulted in increased AVP but decreased CRH expression. Acute LPS administration raised the expression of both AVP and CRH. However, both types of immune challenges increased ACTH and corticosterone levels (Grinevich *et al.*, 2002).

The relationships between elevations in peripheral cytokine levels and HPA axis activation in humans have yielded somewhat inconsistent results. For example, Capuron et al. (Capuron *et al.*, 2003b) evaluated the relationship between initial HPA response to IFNα infusion in patients undergoing treatment for malignant melanoma. Heightened ACTH and cortisol responses to the first IFNα infusion were associated with an increased risk of depression, suggesting that a sensitivity of the HPA axis to immune challenge was associated with vulnerability to depression. However, chronic immune activation has not been reliably associated with HPA axis activation in either humans or animals (Capuron *et al.*, 2003b; Miller *et al.*, 2009), although elevated nocturnal cortisol levels have been shown (Bower *et al.*, 2005; Raison *et al.*, 2010; Rich *et al.*, 2005).

A variety of aspects of immune activation appear to disrupt GR distribution and function, which may account for failure of feedback inhibition of the HPA axis (glucocorticoid resistance) and elevated nocturnal plasma cortisol concentrations (Figure 5). In fact, reduced responsiveness of GR to cortisol has been hypothesized to be part of the pathophysiology of depression (Pariante *et al.*, 1995) as well as inflammatory disorders (Pace *et al.*, 2007a). Under normal physiological conditions, GR is maintained in an inactive state by binding to chaperone proteins, including heat shock proteins 70 (hsp70) and 90 (hsp90) as well as FK506 binding proteins 51 and 52 (Pratt *et al.*, 2006;Tatro *et al.*, 2010) (Figure 5). On binding of glucocorticoids such as cortisol, GR dissociates from chaperone proteins and translocates to the nucleus where it functions as a regulator of gene transcription primarily through its interactions with glucocorticoid response elements (GRE) in promoters of genes (Kumar and Thompson, 2005). GR transcriptional activity is terminated on unbinding of glucocorticoids and re-association with chaperones.

A wide range of studies have suggested that cytokines including TNFα, IL-1α, IL-1β, IL-2, IL-6, and IFNα inhibit GR function leading to glucocorticoid resistance [for comprehensive reviews, see Pace et al. (Pace *et al.*, 2007b; Pace and Miller, 2009)] (Figure 5). For example, TNFα binds to its receptor and triggers a signal transduction cascade that activates IκB kinase β (IKKβ or IKK2) which, in turn, phosphorylates the IκB – NF-κB dimer, releasing NF-κB. The latter, then translocates to the nucleus where it interferes with GR binding to GRE segments via protein-protein interactions (McKay and Cidlowski, 1999). Similarly, IFNα, along with other cytokines, binds to types I and II cytokine receptors resulting in phosphorylation of Janus kinase-1 (Jak1) which activates STAT5, which, like NF-κB, inhibits GR-GRE interactions through protein-protein interactions in the nucleus (Hu *et al.*, 2009; Rogatsky and Ivashkiv, 2006). Finally, IL-1 receptor activation results in mitogen activated protein kinase kinase (MKK)3/6 and MKK4/7 activation. These complexes activate p38 MAPK and c-Jun N-terminal kinases (JNK), which can phosphorylate GR impeding its nuclear translocation. JNK

also phosphorlates cJUN, which associates with cFOS to form the AP-1 complex, which also interferes with GR-GRE interactions (Pace *et al.*, 2007a; Pace *et al.*, 2007b).

3.4 Stress and Immunity

Depression is clearly a stress-sensitive disorder, and both early life stress such as abuse (Heim *et al.*, 2008; Heim and Nemeroff, 2001a; Heim and Nemeroff, 2001b) and recent stressors (Hilsman and Garber, 1995) increase risk for depression. The actual causal mechanisms for the relationships between stress and depression are unknown. However, recent research suggests that stress-induced immune activation may play an important role. As an example, peripheral monocytes from healthy volunteers exposed to a public speaking stressor (referred to as the Trier Social Stress Test) and mental arithmetic have increased NF-κB – DNA binding (Bierhaus *et al.*, 2003). Both IL-6 response and NF-κB – DNA binding in response to an acute social stress have also been shown to be increased in persons with depression (Pace *et al.*, 2006). In addition, chronic stressors from a variety of sources appear to enhance immune activation (Miller *et al.*, 2009).

Recent evidence also illuminates the stress – immune activation – depression linkage. Early childhood maltreatment has long been associated with risk for depression (Heim *et al.*, 2008). A recent study by Danese et al. (Danese *et al.*, 2009) attempted to elucidate whether early adversity and subsequent risk are associated with enduring abnormalities in stress-sensitive biological systems. This study was part of a 32-year prospective longitudinal study of 1037 persons in New Zealand assessed at intervals beginning in early childhood. At age 32 years, participants were assessed for the presence of major depression, inflammation (as indicated by CRP >3 mg/L), and the indicators of cardiometabolic risk factors, including hypertension, total cholesterol, reduced HDL, elevated glycated hemoglobin (indicating evidence for altered glucose metabolism), and low maximum oxygen consumption. Those who had been exposed to childhood adversity showed not only increased likelihood of depression, but also elevated CRP and metabolic risk markers. This suggests that early adversity has enduring effects not only on risk for depression but also immune and metabolic dysregulation. These data are also consistent with other studies suggesting a link between early life stress, immune activation, and depression. For example, Pace et al. (Pace *et al.*, 2006) found that male patients with major depression who had early life stressors exhibit enhanced IL-6 response and NF-κB – DNA binding in response to the Trier Social Stress Test in comparison to non-traumatized depressed controls. Of significance is that baseline IL-6 levels in the traumatized sample were at about the same level as the maximal response to the social stressor in the non-traumatized controls, suggesting that traumatized depressed persons have chronic elevation in IL-6 levels. These findings support a link between major depression, early life stress, and chronic immune activation, and may elucidate a causal mechanism for the association of early trauma and subsequent negative health outcomes.

3.5 The Effects of Antidepressant Treatments on Immune Function

Antidepressants appear to inhibit immune activation via several mechanisms. Many studies of antidepressant effects *in vitro* and *in vivo* have shown reductions in pro-inflammatory factors such as IL2, IL-6, TNFα, and IFNγ (Basterzi *et al.*, 2005; Bengtsson *et al.*, 1992; Kubera *et al.*, 2000a; Kubera *et al.*, 2000b; Kubera *et al.*, 2000c; Kubera *et al.*, 2001a; Kubera *et al.*, 2001b; Lanquillon *et al.*, 2000; Maes *et al.*, 1999; Mohr *et al.*, 2001; Obuchowicz *et al.*, 2006; Seidel *et al.*, 1995; Sluzewska *et al.*, 1995; Song *et al.*, 1994; Szuster-Ciesielska *et al.*, 2003; Zhu *et al.*, 1994; Zhu *et al.*, 1998) (for a review, see Miller et al. (Miller *et al.*, 2009)), although the variability in the data may be accounted for a number of methodological differences (Muller and Schwarz, 2007). One study also found reductions in TNFα levels in severely depressed patients undergoing electroconvulsive therapy (Hestad *et al.*, 2003). The preponderance of evidence suggests that antidepressant treatment induces a shift from Th1

(pro-inflammatory) to TH2/TH3 (anti-inflammatory) processes (Muller and Schwarz, 2007). For example, several studies have demonstrated a reduction in the ratios of IFNγ to IL-10 (Kubera *et al.*, 2001a; Maes *et al.*, 1999; Szuster-Ciesielska *et al.*, 2003) and IL-4 (Myint *et al.*, 2005), as well as an increase in the Th3 molecule transforming (or tumor) growth factor β1 (Myint *et al.*, 2005). Antidepressants also appear to alter the expression of PGE2 and NO. As noted earlier, brain cytokine release, including IL-1α/β (Anforth *et al.*, 1998), IL-6 (Bluthe *et al.*, 2000b), and TNFα (Bluthe *et al.*, 2000a) stimulate endothelial cells in small blood vessels to release prostaglandin E2 (PGE2) and NO, which are important mediators of sickness behavior (Dantzer, 2009). One study (Yaron *et al.*, 1999) showed that fluoxetine and amitriptyline significantly inhibited NO and PGE2 release in synovial tissue exposed to LPS or IL-1α and TNFα. Interestingly, the effects of antidepressants on pro-inflammatory cytokine and related mechanisms may be direct and may not depend on the effects of these drugs on monoamines. For example, amitriptyline and nortriptyline suppress LPS-induced IL-1β and TNFα release in mixed glial cultures (Obuchowicz *et al.*, 2006), suggesting a direct action of the antidepressants on pro-inflammatory cytokines.

Antidepressants also appear to counteract the adverse effects of cytokines on HPA axis function. Most antidepressant treatments, including antidepressant drugs and electrically-induced seizures, increase signal transduction via protein kinase A (PKA) (Duman *et al.*, 1999; Nestler *et al.*, 1989). Transductional activation of PKA by cyclic AMP causes the PKA tetramer to dissociate into regulatory and catalytic subunits (Shelton, 2007). The latter phosphorylates cyclic AMP response element binding protein (CREB), resulting in translocation to the nucleus it interacts with cyclic AMP response elements (CRE) in the promoter regions of genes, including the gene for GR (Eickelberg *et al.*, 1999; Penuelas *et al.*, 1998). PKA phosphorylates GR, which appears to increase GR – GRE interactions and GRE-dependent gene expression. Enhancement of GR activity may be one of the principal mechanisms for normalization of HPA function by antidepressants (Pariante *et al.*, 1995; Plotsky *et al.*, 1998). Signaling via PKA also appears to negatively interact with both NF-κB and p38 MAPK signaling pathways (Pace *et al.*, 2007a), which would be expected to enhance GR signaling. Notably, defects in PKA expression and signaling relative to controls have been noted in both peripheral and brain tissue samples from depressed persons (Akin *et al.*, 2005; Manier *et al.*, 1996; Pandey *et al.*, 2005; Pandey *et al.*, 2007; Shelton *et al.*, 1996; Shelton *et al.*, 1999; Shelton *et al.*, 2009). Reduced PKA activity has been hypothesized to affect GR expression, which would be normalized by antidepressants that enhance PKA-dependent signal transduction (Shelton, 2007).

3.6 Anti-inflammatory Drugs and Cytokine Antagonists as Antidepressants

3.6.1 COX-2 Inhibitors—In spite of considerable evidence linking immune activation and inflammation with depression, surprisingly little research has examined the direct effects of drugs that act on these systems in depressed patients. One target of investigation has been the antagonists of cyclooxygenase (COX) enzymes (also known as prostaglandin-endoperoxide synthase and prostaglandin G/H synthase). COX enzymes are involved in the conversion of arachidonic acid to prostaglandins and eicosanoids (e.g., thromboxanes), which are important mediators of local inflammatory responses (Rao and Knaus, 2008). Both COX-1 and -2 metabolize arachidonic acid to prostaglandin H2 which is a precursor to prostaglandins, prostacyclin, and thromboxanes. Inhibitors of COX-2 are well-known as systemic anti-inflammatory agents (Rao and Knaus, 2008). COX-2 activity is increased by pro-inflammatory cytokines, particularly IL-6, and itself activates the release IL-1β and TNFα (Muller and Schwarz, 2007). A significant downstream product of COX-2 activation is PGE2, which is a significant mediator of sickness behavior as noted above (Dantzer, 2009). Several studies have shown an increase in prostaglandin secretion, including PGE2 in CSF (Linnoila *et al.*, 1983), serum (Calabrese *et al.*, 1986), and saliva (Nishino *et al.*, 1989; Ohishi *et al.*, 1988) of depressed

patients (Muller and Schwarz, 2007). One study also demonstrated increased mitogen-stimulated PGE2 release from whole blood samples in depressed patients compared to controls (Song *et al.*, 1998). Given this evidence, COX-2 inhibition represents a logical target for depression treatment.

The beneficial effects of COX-2 inhibitors in animal models of depression have been documented (Guo *et al.*, 2009; Kumari *et al.*, 2007; Myint *et al.*, 2007). However, one of the earliest observations of an antidepressant effect of COX-2 inhibitors in humans came not in a study of depression *per* se, but an open-label assessment of the effects of the COX-2 antagonist rofecoxib in patients with osteoarthritis (Collantes-Estevez and Fernandez-Perez, 2003). This study was an investigation of the effects of switching from the COX-2 inhibitor celecoxib to rofecoxib in 2228 patients and was intended to determine moderators of response to rofecoxib switch. Patient characteristics (moderators) identified in multivariate analysis as predictive of a favorable response to rofecoxib included age, obesity, depressive symptoms, co-morbid diabetes, and OA severity. A total of 15% of osteoarthritis patients were determined to be depressed at baseline, which declined to 3% during rofecoxib treatment. This was followed by an open-label study of the effects of the non-selective COX-1 and -2 antagonist acetylsalicylic acid (aspirin) added to fluoxetine, which increased remission rates in depressed patients previously nonresponsive to fluoxetine alone (Mendlewicz *et al.*, 2006). The first controlled clinical trial of a COX enzyme inhibitor was a prospective, double-blind, add-on trial in 40 patients with major depression comparing the COX-2 selective antagonist celecoxib (400 mg. per day) versus placebo added to the norepinephrine reuptake inhibitor antidepressant reboxetine (4–10 mg. per day) for 6 weeks (Muller *et al.*, 2006). Although both groups improved, the celecoxib plus reboxetine group experienced greater improvement in depression scores compared to the reboxetine-alone group. These studies suggest a benefit of COX inhibitors added to antidepressant medications in depression, although monotherapy trials of COX-2 antagonists in depression have not been published.

3.6.2 TNF Receptor Antagonists—In recent years, TNF receptor inhibitors have been developed to treat inflammatory diseases such as rheumatoid arthritis, Chrohn's disease, and psoriasis, and include monoclonal antibodies (infliximab, adalimumab, golimumab, and certolizumab pegol) and the TNF receptor fusion protein etanercept. Although these treatments have not been tested in a primary depressed sample, the effects of etanercept on depressive symptoms in patients with inflammatory disease have been tested. In one study (Tyring *et al.*, 2006b), 618 patients with moderate to severe psoriasis received double-blind treatment with placebo or 50 mg twice weekly treatment with etanercept, a recombinant DNA construct antagonist of the TNF receptor, or placebo for 12 weeks. Psoriasis is an inflammatory disease affecting the skin and other tissues with a relatively high rate of depression (Akay *et al.*, 2002; Krueger *et al.*, 2001). Efficacy endpoints included measures of fatigue (the Functional Assessment of Chronic Illness Therapy Fatigue [FACIT-F] and depression (the HRSD and the Beck Depression Inventory [BDI]). Patients on etenercept had greater improvements in depression (HRSD and BDI) and fatigue (FACIT-F) than those on placebo (although the differences in depression ratings were relatively modest). Improvements in depression were not particularly associated with reduction in psoriatic plaques or joint pain, suggesting a primary effect of TNF antagonism on depression (Tyring *et al.*, 2006b). This finding was confirmed in subsequent studies in which etanercept was administered to psoriasis patients over a 54 (Dauden *et al.*, 2010) or 96 week period (Krishnan *et al.*, 2007). Similar results on depression were shown in an etanercept study in rheumatoid arthritis patients (Kekow *et al.*, 2010). Recent studies have also suggested a benefit of infliximab, a TNFα monoclonal antibody, on depressive symptoms in patients with inflammatory diseases (Feldman *et al.*, 2008; Lichtenstein *et al.*, 2002). To date, however, there have been no published studies of etanercept, infliximab, or other TNFα antagonists in depressed patients without inflammatory diseases.

3.7 Immune Activation, Oxidative Stress, and Depression

As described earlier, immune activation of white blood cells, neurons, and glia activates the synthesis of reactive chemical species such as NO, superoxide (O_2-), and peroxynitrile (ONOO−), which contribute to the cytotoxic effects of pathogens (Nathan and Shiloh, 2000). Under normal circumstances, intracellular oxidative stress is buffered through the reducing action of a number of molecules, particularly glutathione. However, high levels of reactive species contribute to cytotoxicity of host cells leading to local tissue necrosis. In addition, chronic immune activation may lead to conditions of heightened oxidative stress.

Heightened oxidative stress has been hypothesized in depression (Cumurcu *et al.*, 2009). Recent studies have shown not only raised indicators of oxidative stress but also reduced anti-oxidant capacity in persons with depression. In one such study (Cumurcu *et al.*, 2009), total oxidative stress and anti-oxidant capacity, measured using standard colometric methods, were examined in 57 persons with major depression and 40 healthy controls. Measures of total oxidative stress were significantly elevated while antioxidant capacity was lower in the depressed group compared to controls. Measures of oxidative stress were positively correlated and antioxidant capacity inversely associated with depression severity. Successful treatment with the antidepressants sertraline, paroxetine, and citalopram were associated with decreases in oxidative stress and enhanced antioxidant capacity. These results are similar to results from other studies, and implicate increased oxidative and nitrosative stress in depression (Maes, 2008).

4.0 Adiposity and Depression

It is clear from the previous discussion that depression is often associated with a pro-inflammatory state, and that body lipid accumulation in the form of WAT is one potential source of inflammatory cytokines. However, is there a link between adiposity, cytokine activation, and depression? Some studies have not found an association between adiposity, inflammation, and depression risk (Murphy et al., 2009; Olszanecka-Glinianowicz et al., 2009; Pan et al., 2008). Moreover, a recent systematic review suggested that the overall association between obesity in general and depression risk is weak (Atlantis and Baker, 2008). However, a more recent meta-analysis of 15 longitudinal studies showed a bidirectional association between depression and obesity (Luppino *et al.*, 2010). That is, obesity increases risk for depression and prior depression increased the likelihood of obesity over time. Another recent study of 2,547 non-depressed, older adults in the Health, Aging, and Body Composition Study, an ongoing prospective community-based cohort study, supports this observation; (Vogelzangs *et al.*, 2009). Assessments in this study include BMI, percent body fat, abdominal obesity measures (waist circumference, sagittal diameter, and visceral fat), and depression (defined as a Center for Epidemiologic Studies Depression scale 10-item score ≥10 at any annual follow-up over 5 years and/or new antidepressant medication use). Over 5 years, both BMI and abdominal obesity predicted onset of depression after adjustment for covariates in men although not in women. However, when BMI and visceral fat were adjusted for each other, only visceral fat was significantly associated with depression onset. The differences between men and women may have to do with the fact that while the women had a higher percentage of body fat, men had more visceral fat at baseline. Other research also supports the significance of visceral (i.e., abdominal) fat. One very large scale epidemiological study found that hip-to-waist ratio, an indicator of abdominal obesity, rather than obesity in general, was associated with risk for depression (Rivenes *et al.*, 2009). Another project conducted a mediational analysis evaluating the relationship between serum inflammatory markers (IL-1β, IL-6, TNFα, MCP-1 [CCL2], and CRP) in 50 physically healthy younger adults with depression and 50 matched non-depressed controls (Miller *et al.*, 2002b). The mediational analysis was conducted in a manner consistent with Baron and Kenny (Baron and Kenny, 1986), in which a mediating role was implied when observed group differences in a variable are attenuated by

a co-variate. The depressed sample showed markedly elevated CRP and IL-6 and had a higher body mass index (BMI) than controls. BMI also was independently associated with IL-6 and CRP but not IL-1β. Significantly, when the relationship between depression and both IL-6 and CRP (but not IL-1β) were adjusted for BMI, the results became non-significant. These results support a mediational role for adiposity in the relationship between depression and IL-6 and CRP elevation (Miller *et al.*, 2002b). A separate analysis of the same data (Miller *et al.*, 2003) suggested an even more complex interplay between depression, obesity, and inflammation. This analysis used structural equation modeling (SEM) yielding a maximum likelihood estimation of the relationship among depression, adiposity, leptin, and inflammation (IL-6, CRP). SEM is a statistical method for estimating causal relationships among associated variables. The advantage of SEM in this instance is that it can estimate the extent of interactions between various factors and identify both predicted and latent (unknown) associations. The SEM was conducted over several analytic phases. The first was a confirmatory factor analysis that identified three underlying constructs: depression, adiposity, and inflammation (IL-6), as predicted. In the second phase, structural modeling was performed to determine the relationships between constructs and evaluated six possible models. The best fit model was one referred to as the "joint fit" model, which suggested that the causal pathway was from depression to adiposity to inflammation. The model also suggested that part of the relationship between adiposity and inflammation could be accounted for by the effects of adiposity on leptin (although it should be noted that other adipocytokines and related molecules were not assessed). As noted by Miller and colleagues, the best fit model suggests that depression causes expanded adipose tissue which leads directly to increases in pro-inflammatory biomarkers (e.g., IL-6) and also indirectly via elevated leptin levels (Miller *et al.*, 2003). It should be noted, however, that this model applies to young, physically healthy depressed persons and may not be applicable to other populations, although baseline depression has been linked to subsequent increases in abdominal obesity in older adults as well (Vogelzangs *et al.*, 2008). However, it does support the interplay between adiposity, cytokines, leptin, and depression.

The linkage between leptin adiposity, and depression has been supported by other research (Lu, 2007). Chronic, unpredictable stressors or social defeat, which induce depression-like behaviors, have been shown to reduce leptin levels in rodents (Lu *et al.*, 2006), a state that mimics leptin resistance found in obesity (Considine *et al.*, 1996). Administration of leptin has been shown to reverse the behavioral effects of both acute and chronic stress that are thought to mimic depression (Lu *et al.*, 2006). However, clinical studies in depressed patients have shown highly variable results, with studies showing increased, decreased, or no differences in leptin levels (Deuschle *et al.*, 1996;Antonijevic *et al.*, 1998;Rubin *et al.*, 2002;Jow *et al.*, 2006;Kraus *et al.*, 2001;Atmaca *et al.*, 2002). This is likely to be related to the clinical heterogeneity of depression and the complexity of leptin response. A deficient response to leptin may be associated with either low leptin levels or down-regulation of leptin receptors (Lu, 2007). Reduced signaling via leptin receptors, whether by leptin insufficiency or decreased receptor responsiveness, may contribute to depressive symptoms.

An association between dyslipidemia and depression has also been reported (Nakao and Yano, 2004; Takeuchi *et al.*, 2009a; Takeuchi et al., 2009b; Tyrovolas *et al.*, 2009). For example, in one study, 1190 older (aged 65 to 100 years) men and women with cardiovascular disease were enrolled in a study intended to evaluate the relationships between elevated serum cholesterol (hypercholesterolemia) and both lifestyle and depression status (Tyrovolas *et al.*, 2009). The signs and symptoms of depression were evaluated using the Geriatric Depression Scale (short form) and hypercholesterolemia was defined as total serum cholesterol > 200 mg/dL or use of lipids lowering medication. Hypercholisterolemic individuals had higher prevalence of obesity (43% vs. 25%), hypertension (76% vs. 57%) and diabetes (25% vs. 17%) and had higher levels of depression compared with participants without hypercholesterolemia. These data are supported by previous studies that have demonstrated an increased incidence of depression in

persons with metabolic syndrome (MetS) in general and hypercholesterolemia in particular (Nakao and Yano, 2004; Takeuchi *et al.*, 2009a; Takeuchi *et al.*, 2009b). In one health behavior study, high cholesterol levels were positively predicted by four variables: presence of major depression, age, body mass index, and the habit of missing breakfast (Nakao and Yano, 2004). Interestingly, another study evaluated the relationship between baseline MetS and the subsequent development of depression in Japanese men followed for one year (Takeuchi *et al.*, 2009a). MetS is defined as being a cluster of medical conditions typically associated with central (abdominal) obesity. These conditions include dyslipidemia (e.g., elevated total and LDL cholesterol reduced HDL cholesterol, and elevated triglycerides), elevations in fasting blood sugar consistent with insulin resistance (type 2 diabetes), and hypertension (Ford *et al.*, 2002; Grundy *et al.*, 2004; NCEP Expert Panel, 2001). MetS is a known risk factor for the development of cardiovascular and cerebrovascular disease. It is also associated with elevations in pro-inflammatory cytokines, particularly TNFα and altered levels of leptin, adiponectin, and resistin (Grundy *et al.*, 2004; Lara-Castro *et al.*, 2007). In fact, the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) includes a pro-inflammatory state as part of the standard definition of MetS (Grundy *et al.*, 2004; NCEP Expert Panel, 2002). Takeuchi *et al* study (Takeuchi *et al.*, 2009a) evaluated 956 Japanese (mean age, 42.7 years). The objective of the study was to test the temporal relationships between MetS and the development of depression and anxiety, controlling for potential confounding factors like age and lifestyle factors. MetS was diagnosed according to the International Diabetes Federation criteria. Depression and anxiety symptoms were assessed at baseline and at a one year follow-up using the Profile of Mood States (POMS) questionnaire and by clinical interview using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Baseline MetS was associated with higher rates of new onset depression but not anxiety in the subsequent year (OR 2.14, 95% CI 1.10–4.17). Of the five individual MetS components examined, only waist circumference was significantly related to new-onset depression (OR 2.08, 1.23–3.50). The authors concluded that MetS, particularly waist circumference, is a risk factor for the subsequent development of depression in men. Taken together, these studies suggest a complex and reciprocal relationship between depression, obesity, MetS, and a pro-inflammatory state.

4.1 The Relationship Between Dietary Constituents and Risk for Depression

The last century has seen a dramatic shift in Western diets toward a much higher n-6:n-3 fatty acid ratio (Mischoulon, 2009). This shift in diet is responsible for the increases in diet- and obesity-related medical conditions, as described earlier. Of note is that the rate of depression appears to parallel this trend (Lavori *et al.*, 1993). A variety of observations suggest that there are relationships between specific constituents of diet, particularly n-3 fatty acids, found in large quantities in fish and fish oil extracts. A number of epidemiological studies have found an association between the prevalence of mood disorders, particularly depression, and the annual consumption of fish (for a review, see Kraguljac et al. (Kraguljac *et al.*, 2009)). Although the data have not been completely consistent, the bulk of the evidence supports a protective effect for fish consumption (Kraguljac *et al.*, 2009). For example, one study based in the central Mediterranean region tested the association between level of fish intake and depressive symptoms in older adults. A total of 1,190 men and women over age 65 were assessed for depression severity using Geriatric Depression Scale (GDS) and food intake using the Food Frequency Questionnaire. People in the lowest one third of depression severity were more educated, physically active, and had a higher level of fish consumption. Even a small increase in fish intake was associated with a significant reduction in depression severity. These data suggest that lifestyle habits, especially fish intake, are associated with a substantial reduction in depression risk in older adults. The relationship between fish consumption and depression risk may be clarified by the results of a recent study (Astorg *et al.*, 2008), which found that whereas fish intake in general was associated with a reduction in depression risk,

intake of so-called fatty fish (i.e., fish with high n-3 fatty acid content, including anchovy, sea bass, carp, dogfish, eel, halibut, herring, mackerel, mullet, fish, roe, salmon, sardine, trout, and fresh tuna) had a greater effect. The benefit of fatty fish intake was lost in smokers, in whom the intake of fatty fish was actually associated with a higher risk of recurrent episodes of depression over an eight year follow-up period, particularly in women. Fish consumption in general and n-3 fatty acid intake in particular has been associated with positive health benefits for a number of diseases, including cardiovascular disease, diabetes, certain forms of cancer, and arthritis (for reviews, see Mazza et al. (Mazza *et al.*, 2007), Juturi (Juturu, 2008), and Ruxton et al. (Ruxton *et al.*, 2004)). The general health benefits of n-3 fatty acids occur via several mechanisms, including positive effects on platelet aggregation. However, a major benefit appears to result from a reduction in inflammatory allostatic load.

These results are supported by a number of other studies of the relationships between diet, particularly the roles of antioxidants and n-3 fatty acids. A major recent report takes off from earlier observations of a possible lower incidence of depression in the Mediterranean region (Birt *et al.*, 2003) and the general health benefits of a Mediterranean diet pattern (MDP). Traditional Mediterranean diets tend to be high in both antioxidants and n-3 fatty acids relative to other Western diets. Sánchez-Villegas et al. (Sanchez-Villegas *et al.*, 2009) conducted a large-scale assessment of the association between adherence to the MDP and the incidence of depression in a sample 10,094 healthy persons in Spain. A baseline assessment was conducted that used a validated 136-item item food frequency questionnaire, from which was derived relative adherence to the MDP. The study also evaluated the relative consumption of foods in several groupings: vegetables, fruit and nuts, cereal, legumes, fish and other seafood, monounsaturated- to saturated-fatty-acid ratio, alcohol consumption, meat or meat products. The main outcome measure was the incidence of depression over a mean of 4.4 years in people free of depression at baseline. Taking the lowest level of adherence to the MDP as the “control” condition, adjusted hazard ratios for depression for the highest categories of adherence to the MDP ranged from 0.49 (95% confidence intervals 0.44 – 0.77) to 0.74 (95% CI = 0.57–0.98), suggesting a strong protective effect for the MDP. A significant protective effect was found for fruits and nuts, legumes, and unsaturated to saturated fatty acid ratio, while whole fat dairy and meat consumption showed an adverse effect. The MDP is generally associated with a number of health benefits, including anti-inflammatory effects and improvements in endothelial function, cardiovascular health, insulin resistance, and MetS (Chrysohoou *et al.*, 2004; Dai *et al.*, 2008; Esposito *et al.*, 2004; Estruch *et al.*, 2006; Panagiotakos *et al.*, 2007; Salas-Salvado *et al.*, 2008; Tortosa *et al.*, 2007). One study in particular found a strong inverse association between adherence to the MDP and serum IL-6 (and a trend for CRP) levels (Dai *et al.*, 2008). In this study, the investigators administered the Willett food frequency questionnaire to 345 middle-aged male twins and assessed adherence to the MDP. Fasting plasma levels of interleukin-6, C-reactive protein, and other cardiovascular risk factors were measured. A mixed-effects regression analyses showed that adherence to the Mediterranean diet was associated with lower plasma IL-6 after adjustment for total energy intake, other nutritional factors, cardiovascular risk factors, and use of medications and supplements. The overall association of adherence to the diet with IL-6 was much stronger than shared genetic or environmental effects. These results indicate that dietary components, including the ratio of n-3 to n-6 fatty acid intake, are associated with both inflammation and risk for depression.

Other dietary components, particularly simple sugars, have adverse effects on body adiposity. The intake of carbohydrates, particularly in the form of high fructose corn syrup, has increased dramatically in recent decades (Marriott *et al.*, 2009). High fructose corn syrup has been singled out as an important contributor to obesity and related diseases (Marriott *et al.*, 2009; Schaefer *et al.*, 2009; Murphy, 2009; Bray, 2008; Brown *et al.*, 2008). What is undeniable is that the consumption of simple sugars, including high fructose corn syrup, have increased dramatically in the last 40 years (Marriott *et al.*, 2009). High fructose corn syrup is an inexpensive sweetener

used in a variety of processed foods, particularly sugared soft drinks (Bray, 2008; Brown *et al.*, 2008). The corn syrup content of sweeteners has more than doubled since 1978 (Marriott *et al.*, 2009). Overall intake of carbohydrates has increased by approximately 42% in the U.S. over this period (Marriott *et al.*, 2009). The unique contribution of fructose to obesity, in contrast to overall carbohydrate loading, has been called into question (White, 2009). However, fructose may be particularly problematic with regard to obesity-related conditions. Body weight in rats is disproportionately higher with equivalent caloric intake of fructose than sucrose (Bocarsly *et al.*, 2010). High fructose intake contributes markedly to dyslipidemia and insulin resistance (Tappy and Le, 2010; Figlewicz *et al.*, 2009; Angelopoulos *et al.*, 2009). The differences between fructose and other sugars appear to be related, in part, to the differential extraction rate of liver on fructose. The extraction of absorbed fructose by the liver is very high as compared to other sugars such as glucose (Schaefer *et al.*, 2009). Therefore, in contrast to other simple sugars, fructose does not contribute substantially to satiety signaling (Moran, 2009) or increases in insulin (Basciano *et al.*, 2005). Fructose loading in the liver increases glycogen and is ultimately metabolized to triglycerides, which are incorporated into very low density lipoproteins. As such, fructose is highly lipogenic (Basciano *et al.*, 2005). Whether in the form of fructose or other simple sugars, high carbohydrate intake is associated with adiposity and associated medical conditions.

4.2 n-3 Fatty Acid Supplementation for Depression

Given the data suggesting a beneficial effect of n-3 fatty acid intake on risk for depression, clinical trials testing the benefits of n-3 supplementation are a logical extension. A number of the earliest studies of n-3 supplementation in mood disorders were in bipolar disorder, suggesting a beneficial effect in depression but not mania (Freeman *et al.*, 2006; Stoll *et al.*, 1999). Subsequent studies in both bipolar and non-bipolar depression yielded highly variable results; however, the designs of these studies were highly variable and many included small sample sizes while others did not use a placebo control (for a review, see Kraguljac et al. (Kraguljac *et al.*, 2009) or Mischoulon (Mischoulon, 2009)). Some of the variability of these data may be related to findings of differential immunoregulatory effects of the two major constituents of n-3 fatty acid extracts EPA and DHA, suggesting that purified EPA might be a better alternative (Maes *et al.*, 2007).

Peet and Horrobin (Peet and Horrobin, 2002) conducted a randomized, placebo-controlled, study of ethyl-EPA at 1, 2, or 4 gm. per day as add-on therapy for 70 persons with major depression who had not responded to an adequate trial of an antidepressant. The 1 mg. per day, but not 2 or 4 mg./day doses showed significantly higher response rates compared to the placebo group (50% versus 29% response). Although preliminary, these data not only indicate that adjunctive EPA may be beneficial in persons with depression not responsive to adequate therapy, but that there may be an optimal dose range for EPA. These results have generally been supported by other studies of ethyl-EPA in depressed samples (Frangou *et al.*, 2006; Mischoulon *et al.*, 2010; Nemets *et al.*, 2002). As an example, Nemets et al. (Nemets *et al.*, 2002) added ethyl-EPA 1 gm. twice per day or placebo to ongoing antidepressant therapy for four weeks in a group of 30 persons with major depression. The patients treated with ethyl-EPA showed greater reduction in depression scores over the treatment period, again supporting a beneficial effect of EPA in depression.

4.3 Are Diet and Adiposity Risk Factors for Childhood Depression?

4.3.1 Adiposity, Inflamamtion, and Obesity-Related Diseases in Childhood—As noted earlier, as with adults, the shifts in diet and reduction of physical activity has led to high rates of overweight and obesity in children and adolescents (Ben-Sefer *et al.*, 2009; James, 2008; Wang and Lobstein, 2006). In fact, there has been an increase of inflammatory diseases associated with overweight in children such as type 2 diabetes, hepatic steatosis (fatty liver

disease), cardiovascular disease, endothelian dysfunction, and MetS typically thought of as diseases of adults in the past (Alisi *et al.*, 2009; Chiarelli and Marcovecchio, 2008; Eyzaguirre and Mericq, 2009; Golden *et al.*, 2009; Molleston *et al.*, 2002; Nanda, 2004; Roberts, 2003; Schuster, 2009; Semiz *et al.*, 2008). The expansion of adipose tissue in childhood is thought to dramatically increase the risk for obesity in adult life, setting a lifetime pattern of overweight, inflammatory allostatic loading, and illness.

In fact, recent research has demonstrated that overweight children show increased evidence of inflammation just like their adult counterparts (Tam *et al.*, 2010; Warnberg and Marcos, 2008 (Steene-Johannessen *et al.*, 2010)). For example, McMurray and colleagues (McMurray *et al.*, 2007) compared inflammatory responses to exercise in overweight youth with normal weight controls. Participants engaged in 10 two minute periods of exercise above the anaerobic threshold; pre- and post-test blood samples were obtained. At baseline, both leukocyte and IL-6 levels were higher in overweight children and increased further with exercise. Monocytes increased in overweight children and remained elevated two hours post-exercise, whereas natural killer, CD4, and CD8 cells declined. These results are consistent with the hypothesis that childhood obesity is associated with a chronic pro-inflammatory state that may be worsened in the short term by high-intensity exercise (McMurray *et al.*, 2007). This has even been confirmed in non-obese children, suggesting that the association between increasing adiposity and indications of inflammation are not limited to more extreme levels of overweight (McVean *et al.*, 2009). These results are also consistent with other research showing increased pro-inflammatory cytokines and alterations in adipocytokines and related molecules associated with obesity in children and adolescents (Jeffery *et al.*, 2008; Sacheck, 2008; Semiz *et al.*, 2008), where the most consistent findings have included high levels of CRP and reduced adiponectin (Korner *et al.*, 2007; Saltevo *et al.*, 2007; Shin *et al.*, 2008; Winer *et al.*, 2006).

The association between altered adiponectin levels and indicators of inflammation was illustrated in a study by Winer et al. (Winer *et al.*, 2006) which examined the relationships between adiponectin and markers of inflammation and adiposity. A sample of 589 obese children and adolescents were administered an oral glucose tolerance test coupled with baseline measures of adiponectin, lipid profile, CRP, IL-6, and leptin. The results showed associations between low adiponectin levels and elevated CRP and aspects of MetS such as reduced LDL and elevated triglycerides, even when controlling for confounding variables such as body mass, sex, ethnicity, and insulin sensitivity. This suggests that altered adiponectin levels may represent an important link between diet-associated obesity and inflammatory biomarkers, and may occur in a manner that is not entirely dependent on increases in body mass.

4.3.2 Adiposity and Depression in Children and Adolescents—The rates of depression and suicide among both children and adults have increased over the last century (Barnes *et al.*, 1986; Klerman *et al.*, 1985; Maughan *et al.*, 2005). Although many factors undoubtedly have contributed to this trend, one important variable may be increases in adiposity (McElroy *et al.*, 2004), which have largely paralleled this trend. The bulk of evidence suggests a bi-directional relationship between adiposity and depression, such that being overweight increases risk for depression and that being depressed enhances risk of elevated adiposity (McElroy *et al.*, 2004; Miller *et al.*, 2002a). In fact, prior depression in childhood is a relatively strong predictor of the subsequent development of obesity, MetS, and inflammatory diseases in adult life (Goodwin *et al.*, 2009; Hasler *et al.*, 2004). One prospective cohort study (Hasler *et al.*, 2004) followed young adults over a period of 20 years and showed that not only was depression associated with being overweight, depression in general and depression with atypical features in particular was related to weight gain over the follow-up period. Another prospective cohort study (Pulkki-Raback *et al.*, 2009) evaluated 921 males and females in childhood (mean age 12) and again in adult life (mean age 33) and found that symptoms of depression in childhood predicted the development of MetS and that MetS in children predicted

depression in females. This suggests a bi-directional relationship between risks for depression and MetS at least for women, although, as discussed earlier, there appears to be a positive association between MetS and level of depression in both men and women (Miettola *et al.*, 2008; Takeuchi *et al.*, 2009a; Takeuchi *et al.*, 2009b). The bi-directionality of the relationship between depression and adiposity is logical. Obesity negatively impacts self-esteem based on cultural aspects of beauty and desirability (Reeves *et al.*, 2008). However, depression also may contribute to risk for depression via effects on physical activity, sleep, and eating behavior (Reeves *et al.*, 2008). However, we would posit that the linkage between depression, adiposity, and inflammation in children is an important area for further research.

Alternatively, do interventions targeting diet and adiposity affect depression risk? One intriguing result has come from a study by Nemets and colleagues (Nemets *et al.*, 2006) of n-3 fatty acid supplementation in children with depression. In this study, depressed children between the ages of 6 and 12 were randomized to receive either 1000 mg. of n-3 fatty acids or a matched placebo containing safflower oil (which contains 74% linoleic acid, an n-6 fatty acid and no n-3) for 16 weeks. The group treated with n-3 fatty acids showed a statistically significant reduction in depression scores compared to placebo. Notably, this effect was relatively slow to accumulate, being evident from weeks 8 to 16. However, the overall effect was relatively robust by endpoint; 70% of children treated with n-3 fatty acids achieved response criteria (defined as a reduction of 50% or more on the Childhood Depression Inventory [CDI]) and 40% achieved a standard definition of remission (CDI < 29). Although the overall sample size was small (N=28), the results are very encouraging and suggest a role for dietary intervention to treat or prevent depression in children.

5.0 The Role of Inactivity in Inflammation and Depression

Adiposity is a major contributor to inflammatory allostatic load and cardiometabolic diseases, but it is by no means the only issue. For example, relative physical inactivity appears to be an important causal factor. Although physical inactivity is strongly associated with obesity, it appears to contribute to risk for inflammation and depression that is relatively independent of adiposity (Bruunsgaard, 2005). Large population-based studies have consistently shown an inverse relationship between physical activity and markers of systemic inflammation (Beavers *et al.*, 2010). Sustained exercise training in both adults and children appears to reduce markers of inflammation, although acute exercise appears to transiently increase inflammation (Ploeger *et al.*, 2009; Buford *et al.*, 2009). It should be noted, however, that even a single bout of exercise improves insulin sensitivity via an increase in insulin-induced translocation of glucose transporters to myocyte cell membranes (Frosig and Richter, 2009). Sustained physical exercise also has been shown to reduce the risk of cardiometabolic diseases (Janiszewski and Ross, 2009). Therefore, adiposity alone is not a sufficient explanation for inflammatory load in the body. In fact Church (Church, 2009) has posited a “low fitness phenotype,” comprising poor diet, overweight, and a sedentary lifestyle. As stated by Church, “there are likely some metabolic disadvantaged individuals with intrinsically low fitness and low oxidative capacity that are also prone to being sedentary due to easy fatigability. For these individuals, there exists a worst case scenario of a sedentary lifestyle superimposed on metabolically disadvantaged muscle resulting in the exaggerated CVD and metabolic risk.” We would also suggest that this is likely to be worsened by the presence of depression. In fact, as noted earlier, structural equation modeling of the relationship between depression, obesity, and inflammation yielded a best fit model which indicated that depression leads to expanded adipose tissue which leads directly to increases in pro-inflammatory biomarkers (e.g., IL-6) in a young, physically healthy sample (Miller *et al.*, 2003).

The relationship between depression, inactivity, adiposity, and inflammation has also been supported by a recent report from the English Longitudinal Study of Ageing (Hamer *et al.*,

2009a). The study sample included 3609 community dwelling older males and females (mean age of 60.5±9.2 years). Depressive symptoms were assessed using the 8-item Center for Epidemiologic Studies Depression (CES-D) scale) along with health behaviors (smoking, alcohol use, and physical activity), body weight, and central adiposity at baseline and at a 2 year follow-up. Elevated depressive symptoms were identified in 12.7% of the sample at baseline and 6.1% at follow-up. Baseline CES-D score was associated with increased CRP and fibrinogen measured 2 years later. Mediational analysis showed a direct association of depressive symptoms on CRP and indirect mediating effects through behavioral risk factors. The fibrinogen effect was not directly related to depression and was entirely explained through indirect mediating effects on health behaviors. When individual health behaviors were examined, a strong protective effect was shown for physical activity on both baseline and follow-up depressive symptoms. Moderate and vigorous physical exercise ≥ 1 time per week reduced depression risk at baseline (OR = 0.60 and 0.44 respectively) and at 2 years (OR = 0.49 and 0.32) (Hamer *et al.*, 2009a). A subsequent analysis showed that physical activity contributed a level of risk for depression and elevated CRP that was independent of other lifestyle determinants (Hamer *et al.*, 2009b). Together, these data suggest a strong interplay of several factors including depression, obesity, inactivity, and inflammation. What is likely to be the case is that each of these factors interacts with the others. For example, a causal path from inactivity to depression could be posited given the relationship between a sedentary lifestyle with both obesity and inflammation. However, depression also may lead to inactivity, as well as other negative lifestyle factors such as smoking and excessive alcohol use that contribute to risk for obesity and inflammation.

6.0 Depression, Immune Dysregulation, and Adiposity: Summary and Conclusions

To this point we can conclude: 1. Many people with medical conditions that are associated with increases in inflammation such as certain form of cancers, rheumatoid arthritis, multiple sclerosis, psoriasis, and cardiovascular disease have elevated rates of depression; 2. Patients with these conditions who are depressed have increased markers of inflammation such as CRP and IL-6 compared to non-depressed persons with the same conditions; 3. Many ostensibly medically healthy persons with depression show elevations in inflammatory markers (e.g., IL-6 and CRP) in the absence of obvious inflammatory disease, consistent with a Th1 immune response; 4. Many of the symptoms of depression (e.g., fatigue, anhedonia, low motivation, HPA axis activation) are similar to symptoms seen in the context of immune activation (sickness behavior); 5. Administration of inflammatory cytokines such as IFNα for the treatment of diseases such as hepatitis C and malignant melanoma induce depressive symptoms in previously asymptomatic individuals; this parallels sickness behavior in animal models but it is almost indistinguishable from clinical depression; 6. Blockade of mediators of depression such as TFNα reduce symptoms of depression in patients with inflammatory disease; 7. Many of the cellular mechanisms involved in immune activation (e.g., serotonin and dopamine depletion and NMDA receptor activation) are related to hypothesized pathophysiological mechanisms for depression. The preponderance of evidence suggests that inflammatory mediators are involved in the generation of depression in certain individuals.

The causes for the activation of the immune system in depression are undoubtedly complex (Maes, 2008) and remain unknown. However, increasing evidence suggests a possible causal link between adiposity, particularly central (abdominal) obesity and both inflammation and depression. Obesity leads to increases in inflammatory cytokines and adipocytokines, and changes in related molecules such as leptin and adiponectin, which may contribute to the development of depression in vulnerable individuals. However, the relationship appears to be bidirectional, such that prior depression seems to increase the risk for subsequent adiposity

(Miller *et al.*, 2002a). Clearly, more research is needed to examine the complex interplay between depression, inflammation, and adiposity, an effect that may be related in part to effects of depression on physical activity (Hamer *et al.*, 2009a; Hamer *et al.*, 2009b). However, the interactions between these systems offer unique opportunities for targeted treatment and prevention strategies, particularly in children and adolescents. For example, there is a pressing need to investigate strategies to disrupt inflammatory signaling in persons with depression who show indication of a pro-inflammatory state (e.g., those with elevated CRP). Research on approaches that alter diet, increasing the intake of n-3 fatty acids, or reducing weight in depressed persons or populations at risk of developing depression (e.g., children of depressed parents) are also needed.

This review has focused on adiposity and inflammation as possible contributing factors for depression. However, several salient facts must be noted. Depression is a complex and multifaceted disease with many contributing factors. This review is not intended to suggest that inflammation or adiposity contribute to depression in all or even most affected people. For example, sickness behavior that lies at the heart of the link between inflammation and depression is often associated with weight loss, not weight gain (Kelley *et al.*, 2003; Tisdale, 2009). In fact, in the context of weight loss associated with cancer (cachexia), IL-6 levels are associated with severe muscle wasting, particularly in the terminal state (Tisdale, 2009). Inflammatory cytokines have been hypothesized to be the proximal causal path mediating the link between cancer cachexia and depression (Illman *et al.*, 2005; Menzies *et al.*, 2005). However, this has implications for the pathways linking inflammatory cytokines and depression. Specifically, there are likely to be multiple paths to increased inflammatory cytokines, including adiposity on one side, or muscle-wasting diseases such as cancer on the other, which may contribute to depression risk. Further, in some people, depression itself may contribute to increased inflammatory cytokines in a manner that is independent of other inflammatory conditions in the body.

Abbreviations

5-HIAA	5-hydroxy indoleacetic acid
5HTT	serotonin transporter
AAAD	aromatic amino acid decarboxylase
ABCA1	ATP-binding cassette transporter-1
ACTH	adrenocorticotropic hormone
AP1	activator protein 1
ATP III	National Cholesterol Education Program’s Adult Treatment Panel III Report
AVP	arginine vasopressin
BDI	Beck Depression Inventory
BH4	tetrahydrobiopterin
BMI	body mass index
CCL	chemokine (CC-motif) ligands
CD4+	t-helper lymphocytes
CD8+	cytotoxic lymphocytes
CDI	Childhood Depression Inventory

CNS	central nervous system
COX	cyclooxygenase
CRE	cyclic AMP response element
CREB	cyclic AMP response element binding protein
CRH	corticotrophin releasing hormone
CRP	c-reactive protein
CSF	cerebrospinal fluid
DAT	dopamine transporter
DHA	docsahexanoid acid
EPA	eicosapentaenoic acid
ERK	extracellular signal-regulated kinases
FACIT-F	Functional Assessment of Chronic Illness Therapy Fatigue
GDS	Geriatric Depression Scale
GR	glucocorticoid receptor
GRE	glucocorticoid response element
HDL	high density lipoprotein
HEK	human embryonic kidney
HPA	hypothalamic-pituitary-adrenal
HRSD	Hamilton Rating Scale for Depression
hsp70	heat shock protein 70
hsp90	heat shock protein 90
IDO	idoleamine 2,3-dioxygenase
IFN	interferon
IKK	IκB kinase
IL	interleukin
IL-1Ra	interleukin 1 receptor antagonist
iNOS (NOS II)	inducible nitric oxide synthase
IRF1	interferon regulatory factor-1
IRS-1	insulin receptor substrate-1
JAK1	Janus kinase-1
JNK	c-Jun N-terminal kinases
KMO	kynurenine 3-monooxygenase
KYN-A	kynurenic acid
LDL	low density lipoprotein
LPS	lipopolysaccharide
MAP	mitogen-activated protein kinas

MCP-1	monocyte chemoattractant protein 1
MDP	Mediterranean diet pattern
MEK	MAPK kinase
MetS	metabolic syndrome
MKK	mitogen activated protein kinase kinase
mmLDL	minimally-modified low density lipoproteins
MYD88	myeloid differentiation primary response gene 88
n-3	omega-3 fatty acid
n-6	omega-6 fatty acid
n-9	omega-9 fatty acid
NF-κB	nuclear factor kappa B
NMDA	N-methyl-D-aspartic acid
NO	nitric oxide
PAMP	pathogen-associated molecular patterns
PGE2	prostaglandin E2
PKA	protein kinase A
POMS	Profile of Mood States
PPARα	peroxisomeproliferator-activated receptor-α
PTX	pentraxin
PUFA	polyunsaturated fatty acid
PVN	paraventricular nucleus
QUIN	quinolinic acid
STAT1a	signal transducer and activator of transcription 1a
TAB	mitogen-activated protein kinase kinase kinase 7-interacting proteins
TH	tryptophan hydroxylase
Th1	T-helper cell 1 (innate) immunity
Th2	T-helper cell 2 immunity
TLR	toll-like receptor
TNFα	Tumor necrosis factor alpha
TGFβ	transforming growth factor beta
UCP-1	Uncoupling protein 1
WAT	White adipose tissue

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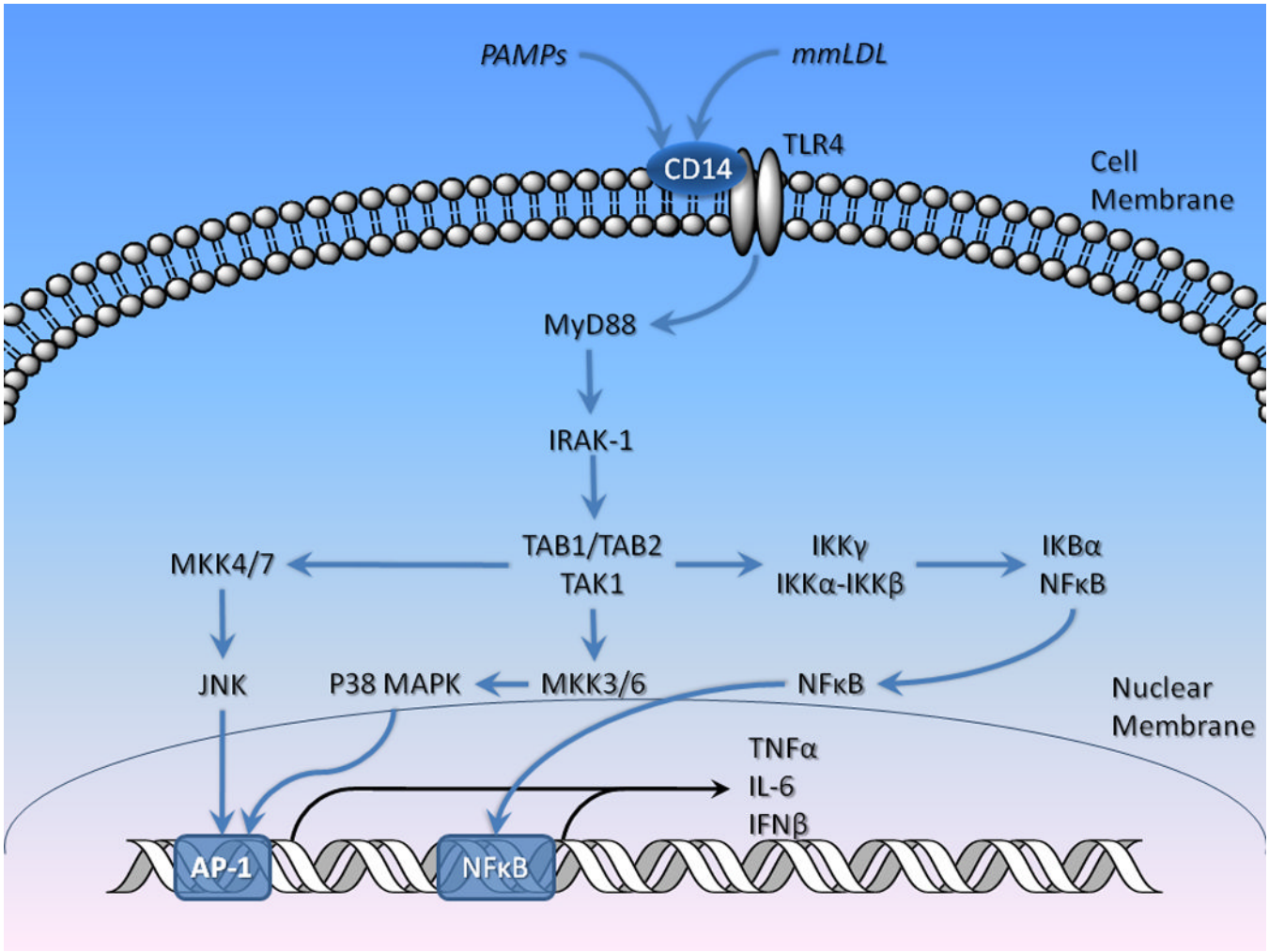

Figure 1. Intracellular mechanisms mediating the immune response: The role of toll-like receptors

The generation of the initial inflammatory response depends on the recognition of specific molecular patters (PAMPs) associated with microorganisms or injured host tissues by pattern recognition receptors such as toll-like receptors (TLRs) and signal transduction cascades linked to important intracellular mediators of immune response including JNK, p38 MAPK, and NF-κB. Activation of TLRs links to a common transductional molecule, myeloid differentiation primary response gene 88 (MYD88), which, in turn, activates mitogen-activated protein kinase kinase kinase 7-interacting proteins (TAB1–4) and mitogen-activated protein kinase kinases (MKK) that activate P38 MAPK and JNK, which interact with AP-1, resulting in transcriptional activation of cytokine genes. TAB proteins also interact with the IKKγ – NF-κB complex, resulting in the release of the transcriptional factor NF-κB.

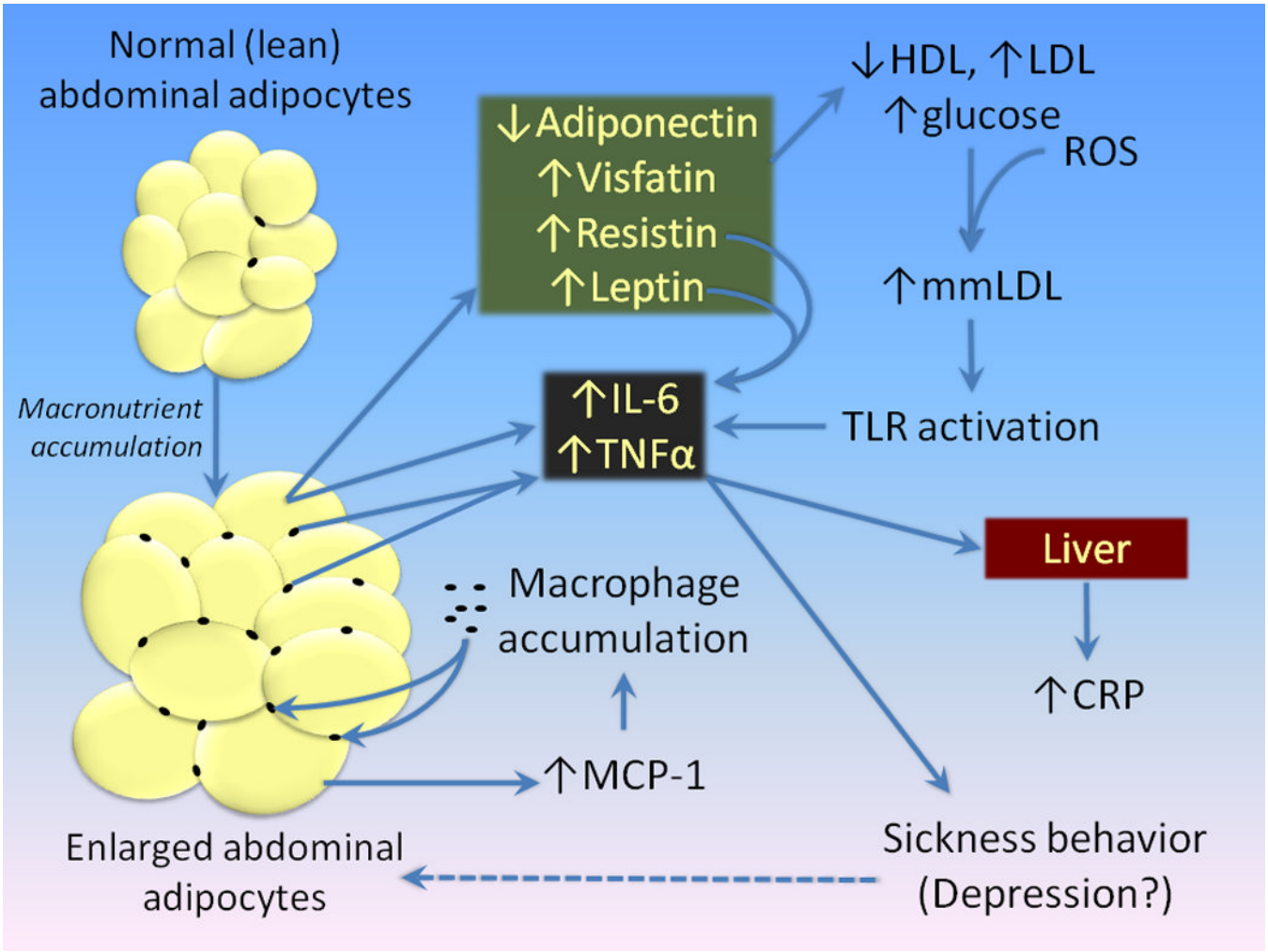

Figure 2. Adiposity and inflammation

High caloric intake in the diet leads to increased accumulations of lipids in adipocytes. Increased lipid content results in an increased release of MCP-1 (CCL2), a chemoattractant that increases the infiltration of macrophages into adipose tissue. Both adipocytes and macrophages release inflammatory mediators such as IL-6 and TNFα into the peripheral circulation. This, coupled with adverse effects on adipocytokines and related molecules such as leptin, resistin, visfatin, and adiponectin is thought to mediate the relationship between accumulation of adipose tissue and conditions such as dyslipidemias and diabetes. Low density lipoprotein cholesterol is oxidized to form minimally-modified LDL's (mmLDL), which also can activate toll-like receptors, further stimulating the production of cytokines. Increases in peripheral cytokines may, then, lead to depression. However, depression may also enhance the accumulation of body fat, further aggravating the process of adipose-induced inflammation.

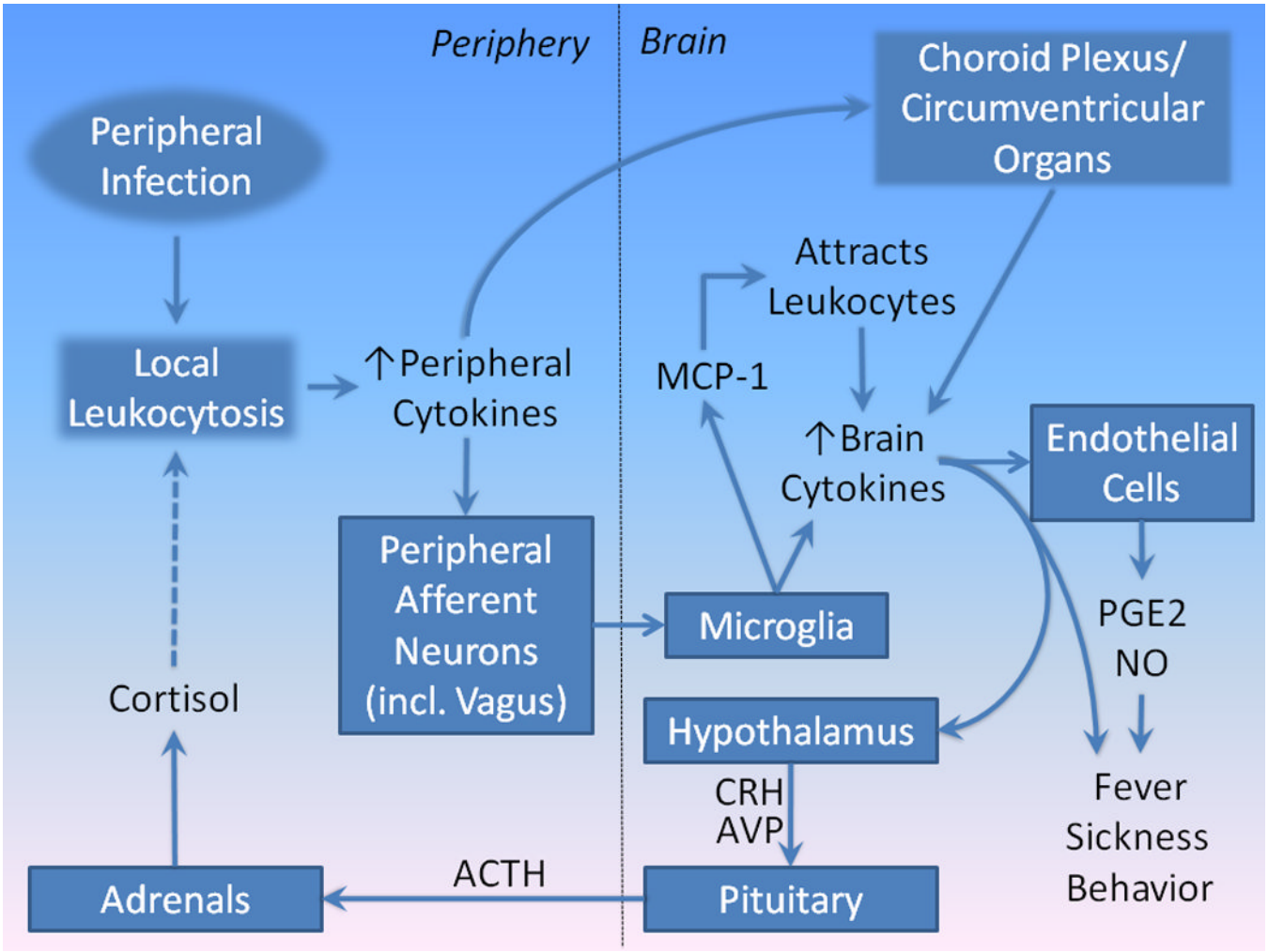

Figure 3. Sickness behavior: Mechanisms mediating activation of brain cytokine signaling by peripheral cytokines

(Adapted from (Dantzer, 2009). The invasion of peripheral tissues by pathogens sets up a local inflammatory response using innate immune cytokine mechanisms. Peripheral inflammation activates brain inflammatory responses by several pathways. First, locally released cytokines activate afferent neurons (e.g., the vagus nerve) that innervate the affected body region. Afferent neurons, then, activate cytokine release from microglia in brain. Activated microglia also produce MCP-1, which attract leukocytes from the peripheral circulation. These leukocytes further increase the local inflammatory response in brain. Second, cytokines released peripherally travel via the circulation and activate leukocytes in the choroids plexus and circumventricular organs, setting up a local immune response, including the diffusion of cytokines into brain tissues. Brain regional cytokine release stimulates endothelial cells in small blood vessels to release PGE2 and NO. The combined effects of cytokines, PGE2, and NO in brain are thought to generate sickness behavior. Cytokines, particularly IL-1β, stimulate the release of CRH and AVP from paraventricular nucleus of the hypothalamus, which activates the release of ACTH from the pituitary, which travels to the adrenals, stimulating the release of cortisol. The latter inhibits immune activation, limiting the score of inflammation both peripherally and centrally.

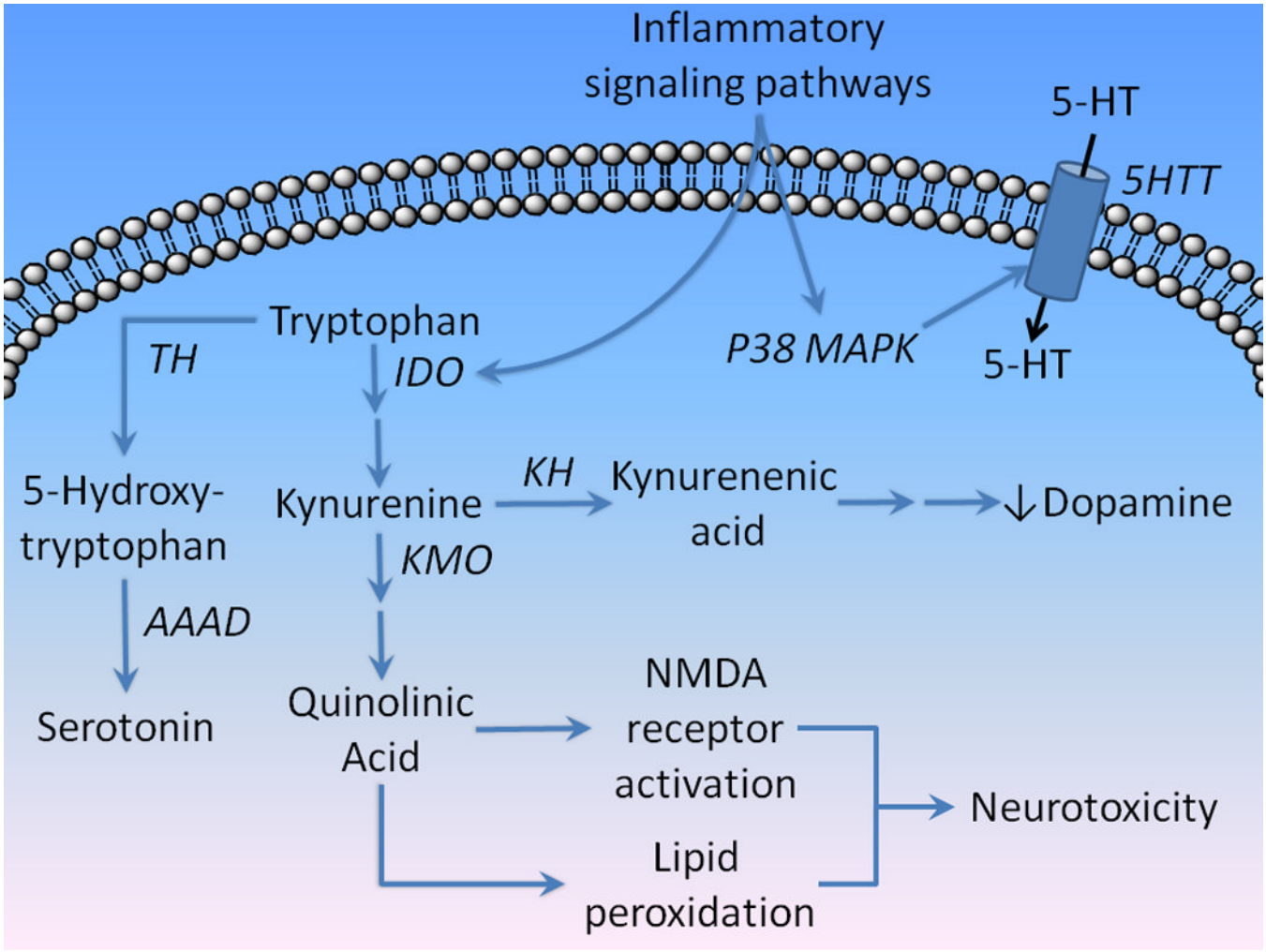

Figure 4. The effects of innate immune activation on serotonin and kynurenines

Inflammatory signaling pathways activate indoleamine 2,3-dioxygenase (IDO) which converts tryptophan to the neuroactive metabolite intermediary kynurenine. IDO activation is thought to compete with tryptophan hydroxylase (TH) metabolism of serotonin (5-HT). Kynurenine is then metabolized by kynurenine hydroxylase to kynurenic acid, which activates α7 nicotinic receptors leading to inhibition of the presynaptic release of dopamine. However, kynurenine is also metabolized via the kynurenine 3-monooxygenase (KMO) pathway to QUIN, a potent activator of NMDA receptors and lipid peroxidation, which is thought to underlie the neurotoxic effects of IDO activation. Inflammatory signals also activate P38 MAPK, which phosphorylates the serotonin transport (5HTT), increasing the uptake of serotonin. (AAAD=aromatic amino acid decarboxylase)

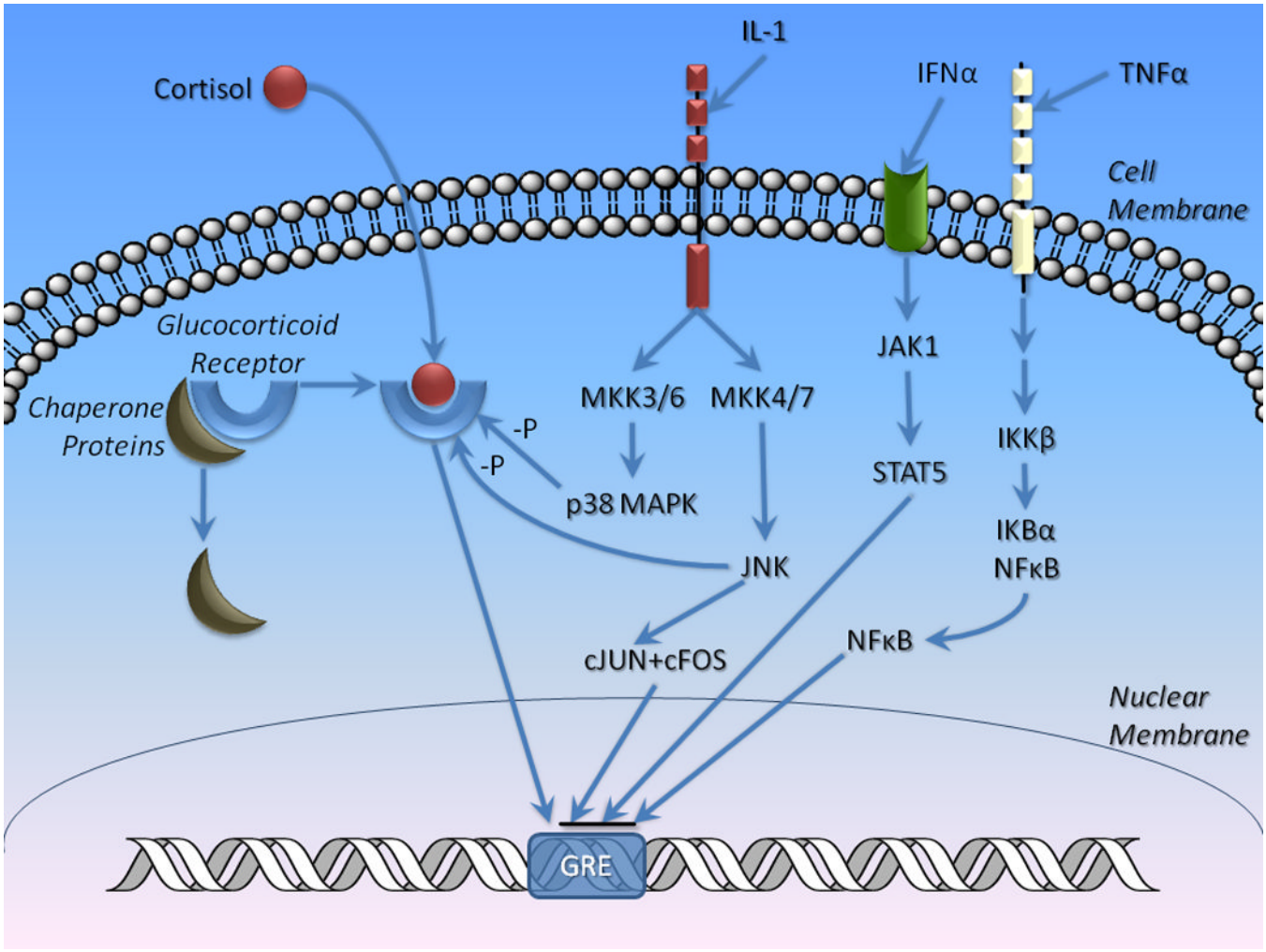

Figure 5. Disruption of gluocorticoid receptor (GR) function by immune activation

Under normal conditions, GR is maintained in an inactive state in the cytosol bound to chaperone proteins, such as hsp70, hsp90, and FK506 binding proteins 51 and 52. The binding of the glucocorticoid receptor to cortisol causes the dissociation of GR from chaperone proteins allowing it to interact with gluococorticoid response elements (GREs) in promoter regions of relevant genes resulting in gene transcription. A variety of cytokines including IL-1, TNFα, and IFNα can disrupt this process. For example, several mechanisms inhibit transcriptional activation of GREs by GR. These include: 1. IL-1 receptor activation of mitogen activated protein kinases (MKKs), leading to phosphorylation of JNK and activation of cJUN; 2. Activation of INF receptors leading to activation of Janus kinase-1 (JAK1) and STAT5; and 3. TNF receptor activation of IκB kinase β (IKKβ) results phosphorylation and dissociation of the IKBα – NF-κB complex. Il-1-induced MKK activation of P38 MAPK also results in GR phosphorylation, which interferes with nuclear translocation.