Cytokines in Depression and Heart Failure

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Objective: There is a convincing body of evidence linking depression, cardiovascular disease, and mortality. There is also growing evidence that depression is a risk factor for congestive heart failure (CHF) and that CHF patients with major depression have higher rates of mortality and repeat hospitalizations. Currently there are no proposed neurobiological or neuroimmune mechanisms for the comorbidity of heart failure and depression. **Methods:** This review focuses on the recent literature about the role of cytokines in CHF and depression as separate conditions. This review also attempts to identify the overlapping immunological mechanisms that have a potential for future research in the pathophysiology of comorbid depression and CHF. **Results:** Results of current studies suggest that cytokines exert deleterious effects on the heart and that soluble tumor necrosis factor (TNF) receptor 2 leads to reversal of the cardiotoxic effects of TNF, although the clinical significance of this is unclear. Major depression has been associated with alteration of various aspects of the innate immune system, including cellular components (such as microphages, neutrophils, and natural killer cells) and soluble mediators (such as acute-phase reaction proteins and cytokines). It is inconclusive whether antidepressants have immunoregulatory effects. **Conclusions:** The literature has not yet addressed the role of cytokines in comorbid depression and CHF. But cytokines may provide a new avenue in understanding brain-body interaction in depression and heart failure. **Key words:** major depression, congestive heart failure, comorbidity, pathophysiology, immunomodulation, cytokines.

CHF = congestive heart failure; CRH = corticotropin-releasing hormone; HPA = hypothalamic-pituitary-adrenal; IHD = ischemic heart disease; IL = interleukin; INF = interferon; LV = left ventricular; mRNA = messenger ribonucleic acid; NK = natural killer; NYHA = New York Heart Association; OR = odds ratio; s = soluble; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor; 5-HT = 5-hydroxytryptamine (serotonin).

INTRODUCTION

Major depression is a common disorder with a lifetime prevalence of 13%. Depression is even more common in patients with ischemic heart disease (IHD), with prevalence rates between 15% and 22%. The high rates of depression in IHD are important because depression has been strongly associated with increased cardiac events and mortality (1–3). Depression has been implicated in the progression of IHD as an independent risk factor in both retrospective and prospective studies. The impact of depression in patients with congestive heart failure (CHF) has been less well studied even though heart failure is an increasingly common consequence of IHD and hypertension and a major cause of morbidity and mortality among the elderly.

Enhanced preventive efforts and advances in the management of acute myocardial infarction, diabetes, and hypertension have led to decreased mortality rates from these disorders but have increased the prevalence of heart failure (4). Heart failure is the fastest growing cardiovascular disorder in the United States. It is the only one increasing in incidence and prevalence (5) and the leading cause of hospital admissions for patients more than 65 years old (6). It is estimated to affect 3% to 5% of those older than 65 years and 10% of those older than 75 years (7). Each year approximately 400,000 new cases of CHF are diagnosed (8). Disease prevalence is expected to reach 10 million cases in the United States alone by the year 2007 (7, 9). It is predicted to become the leading cause of death by 2020 (World Health Organization).

DEPRESSION IN CONGESTIVE HEART FAILURE

Previous studies on quality of life in patients with CHF have showed correlations of symptom severity with negative affect. Depending on the study, the incidence of depression has been reported to be from 15% to 36% (10–13). Perhaps because of design limitations, these studies did not show significant effects

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Received for publication February 5, 2001; revision received March 4, 2002.

DOI: 10.1097/01.PSY.0000058372.50240.38

0033-3174/03/6502-0181

of depression on health outcomes; however, they suggest that depression may be an important and neglected problem in CHF patients.

Most recently Jiang et al. (14), in a study of 374 consecutive patients hospitalized with heart failure, reported prevalences of 14% and 35% for major and minor depression, respectively. In this study patients with a positive Diagnostic Interview Schedule rating and Beck Depression Inventory score of ≥10 were classified as having major depression. Patients with a negative Diagnostic Interview Schedule rating and a score of ≥10 on the Beck Depression Inventory were classified as having minor (mild) depression. They also reported that CHF patients with major depression had twice the mortality rate at 3 months (odds ratio (OR) = 2.5; $p = .08$) and 1 year (OR = 2.23; $p = .04$). Major depression was associated with increased admissions at 3 months (OR = 1.9; $p = .04$) and 1 year (OR = 3.07; $p = .005$) compared with CHF patients who were not depressed. These increased risks were independent of age, New York Heart Association (NYHA) class, baseline ejection fraction, and ischemic origin of CHF. Abramson et al. (15) reported that depression was independently associated with a substantial increase in the risk of developing heart failure among older persons with isolated systolic hypertension. In their study of 4538 patients aged more than 60 years who were enrolled in the Systolic Hypertension in the Elderly Program (SHEP), they found that depressed persons had a more than two-fold higher risk of developing heart failure compared with nondepressed persons (hazard ratio = 2.59).

We are currently conducting a prospective study designed to investigate the prevalence of depression and its effect on functional status, morbidity, mortality, and healthcare utilization in patients with end-stage heart failure. Our preliminary data indicate that depression is strongly associated with functional and symptom outcomes in elderly primary care patients and patients with advanced heart failure (16, 17).

With evidence mounting that there is an association between depression and CHF outcomes, the possible pathophysiologic mechanisms underlying this association should be addressed. Because the etiology of CHF is often associated with IHD, potential pathophysiologic mechanisms may be inferred from the IHD literature. Nonadherence to treatment regimens due to depression is the most well-documented mechanism by which depression produces adverse outcomes in coronary artery disease (18, 19). There are at least three other proposed mechanisms for the contribution of depression to the pathogenesis of IHD (20, 21): 1) *increased hypothalamic-pituitary-adrenal (HPA) function*, demonstrated by elevated corticotropin-releasing factor, blunting of the adrenocorticotropic hormone response to corticotropin-releasing factor, elevated cortisol levels, and *sympathoadrenal hyperactivity*, as evidenced by hypersecretion of norepinephrine and an elevated plasma norepinephrine concentration; 2) *alteration in autonomic nervous system activity*, as demonstrated by reduced heart rate variability; and 3) *disturbance in platelet activation mechanisms*. There is a body of literature about inflammation in IHD, but links to depression have generally not been made. This review focuses on the possible role of cytokines in CHF and depression.

MAJOR PROPERTIES OF CYTOKINES

In the early 1980s cytokines were characterized as communication molecules between immune cells and endothelial cells. Their key role is in the regulation of immune responses and the coordination of the host response to infection. On the basis of their primary biological activities, cytokines are often grouped as lymphocyte growth factors, mesenchymal growth factors, interferons, chemokines, and colony-stimulating factors. By their role in inflammation, cytokines are classified as proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF), and anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13. The typical cytokine cascade includes induction of an early class of cytokines, which then leads to increased production of later cytokines. For example, IL-1 initiates the cytokine cascade by stimulating the release of IL-2, IL-6, and TNF (22).

The specificity of cytokine action is provided by unique cytokine receptors. Interaction of cytokines with cytokine receptors is a necessary component of their physiologic role. Cytokine receptors exist in membrane-bound and soluble forms. A soluble receptor for a particular cytokine can inhibit the biological activity of the cytokine by inhibiting the binding of that cytokine to its membrane-bound receptor. For example, a soluble TNF receptor (eg, etanercept) decreases the biological activity of TNF by inhibiting binding of the cytokine to its specific surface receptor. In rare instances, however, the binding of the cytokine to its soluble receptor can form a complex that enhances the biological activity of the cytokine (eg, IL-6 forms a biologically active complex by binding to soluble IL-6 receptors). Typically there is a regulatory control between the cytokines and specific cytokine inhibitors. Under physiologic conditions, cytokine inhibitors serve as immunomodulatory elements that limit the potentially injurious effects of sustained inflammatory reactions. Under pathologic conditions, anti-inflammatory mediators may either 1) provide in-

sufficient control over proinflammatory activities in immune-mediated diseases or 2) overcompensate and inhibit the immune response and expose the host at risk to systemic infection. The overall effect of any cytokine depends on the timing of cytokine release, the local milieu in which it acts, the presence of competing or synergistic elements, cytokine receptor density, and tissue responsiveness to each cytokine (23).

The pivotal role of cytokines in immunoregulation has recently been explored in variety of medical conditions, including rheumatoid arthritis (24), CHF (25), neurological diseases (26), and psychiatric disorders (27). Apples et al. (28) recently reported an association between the depressive symptomatology of patients with coronary disease and serological markers of inflammation. They found that depressive symptomatology in angioplasty patients was associated with increased levels of IL-1β and IL-6 and antibody titers of *Cytomegalovirus* and *Chlamydia pneumoniae*.

CONGESTIVE HEART FAILURE AND CYTOKINES

Heart failure is a complex cascade of dynamic events controlled and influenced by many neurohumoral factors. Traditionally heart failure has been viewed as a hemodynamic disorder. However, more recent studies have suggested that neurohormones and neural modulators play an important role in the pathogenesis of heart failure because of the direct toxic effects these molecules exert on the heart and circulation. These include neurohormones (eg, norepinephrine, angiotensin II, and endothelin-1) and immunomodulators (cytokines).

The cytokine hypothesis of heart failure (25) proposes that heart failure progresses because the cytokine cascade activated after myocardial injury exerts deleterious effects on the heart and circulation. This hypothesis implies that the overexpression of cytokines contributes to the progression of heart failure once left ventricular (LV) dysfunction is present, but it does not mean that cytokines per se initiate heart failure. After an initial myocardial injury by myocardial infarction, hemodynamic overload, or inflammation, various secondary mediators such as cytokines and neurohormones act on the myocardium and stimulate myocardial remodeling through myocyte hypertrophy, apoptosis, and altered gene expression in cardiac myocytes (29).

There are several hypotheses with respect to the source of proinflammatory cytokines in heart failure. One hypothesis is that activation of the immune system is responsible for cytokine elaboration, which happens in response to some forms of tissue injury (as described above) or possibly some unknown stimulus to the immune system. A second hypothesis is that the failing heart itself may be the source of TNF-α production in heart failure and that elevated levels of TNF-α represent spillover of cytokines that were produced locally within the myocardium, leading to secondary activation of the immune system (30). This is then capable of amplifying the cytokine signal in the periphery. The third hypothesis is that decreased cardiac output in heart failure leads to the elaboration of TNF-α by underperfusion of systemic tissues. An extension of this hypothesis is that gut wall edema allows translocation of endotoxin, which activates cytokine production (31).

The effect of cytokines on the heart is initiated by specific receptors on the myocyte. In the case of TNF-α, ligand-receptor signaling is initiated by binding of TNF-α to a lower-affinity, 55-kD receptor (TNFR1) or a higher-affinity, 75-kD receptor (TNFR2). TNF receptors in heart failure are capable of receptor shedding; that is, they are cleaved from the cell membrane and subsequently exist in the circulation as circulating soluble receptors, referred to as sTNFR1 and sTNFR2. In cell cultures these soluble receptors have been shown to retain their ability to bind to TNF-α and inhibit its cytotoxic activity. It is believed that the role of circulating soluble binding proteins (such as sTNF-binding proteins) in vivo is to serve as biologic buffers capable of neutralizing the highly cytotoxic activities of cytokines (30).

Many aspects of CHF have been linked to the biological effects of cytokines. Some of the proposed mechanisms by which cytokines damage the heart are based on the hypothesis that TNF-α is a mediator of sepsis-induced alterations in the diastolic mechanical properties of the myocardium. Administration of TNF-α suppresses myocyte contractility, increases apoptosis, and decreases interstitial matrix (32). This promotes LV dysfunction (33), pulmonary edema (34), and cardiomyopathy in humans (35) and LV remodeling in dogs (32). Although the most consistently increased cytokines in heart failure have been IL-6 and TNF-α, other cytokines, such as IL-1β and IL-2, have also been associated with the pathogenesis of heart failure (36).

Cytokines are increasingly considered to be a significant factor in the pathogenesis of heart failure and possibly the functional status of heart failure patients. Advanced heart failure is correlated with a progressive increase in peripheral circulating levels of TNF-α. Overexpression of TNF-α in myocardium may be one of several maladaptive mechanisms responsible for the progressive cardiac decompensation and remodeling that occur in advanced heart failure.

High blood levels of TNF-α have been found to correspond to the severity of heart failure symptoms. Investigators for the Studies of Left Ventricular Dysfunction (SOLVD) in patients with heart failure reported a trend toward increasing mortality with in-

creasing levels of TNF-α (37). In vitro studies have shown that TNF-α produces negative inotropic effects in isolated contracting cardiac myocytes by altering calcium homeostasis. Soluble TNF receptors (sTNFR1 and sTNFR2) that bind to TNF-α can both prevent and reverse the negative inotropic effects of TNF-α in isolated contracting cardiac myocytes. However, elevated levels of sTNFR2 have also been shown to correlate with adverse short-term clinical outcomes in hospitalized heart failure patients (38). The significance of this finding is unclear because soluble TNF receptors may also be considered protective of the heart because they bind to TNF-α and inactivate it.

IL-6 is a multifunctional proinflammatory and vasodepressor cytokine that mediates both immune and inflammatory responses. IL-6 and TNF-α can produce myocardial dysfunction and abnormal endothelium-dependent vasodilatation and muscle wasting. It has been shown that IL-6 spillover in the peripheral circulation increases with the severity of CHF and that plasma IL-6 increase is mainly associated with activation of the sympathetic nervous system. High plasma levels of IL-6 were found to be a predictor of mortality in patients with NYHA class I through IV heart failure independent of LV ejection fraction (39). Another study reported that increased serum IL-6 was identified as a powerful independent predictor of the combined end point of death, new heart failure episodes, and the need for heart transplantation (40).

In a recent study on the prognostic importance of proinflammatory cytokines, investigators found that increased levels of TNF-α, sTNFR1, sTNFR2, and IL-6 predicted 24-month mortality in 152 patients with CHF. sTNFR1 was found to be the strongest and most accurate prognosticator, independent of established markers of CHF severity (41). The Vesnarinone Multicenter Trial (VEST), which involved 1200 patients, revealed that cytokines (TNF and IL-6) and their cognate soluble receptors (sTNFR1 and sTNFR2) were independent predictors of increased mortality in patients with advanced heart failure and that circulating levels of cytokines were modified by age, sex, and cause of heart failure. The investigators also reported that cytokines were consistently higher in patients with ischemic cardiomyopathy than in patients with dilated cardiomyopathy (42). This is contrary to the previous report by Munger et al. (43) that cytokine concentrations did not differ by the cause of heart failure.

CYTOKINES AS POTENTIAL THERAPEUTIC TARGETS IN HEART FAILURE

Because it has been shown that cytokine production and activity can be antagonized (eg, high amounts of soluble TNF receptors function as specific inhibitors of TNF activity), one natural question that arises is whether cytokine bioactivity can be modulated as a treatment modality in patients with heart failure. Treatment with two TNF blockers, etanercept (soluble TNF-α) and infliximab (chimeric antibody), has been shown to have strikingly beneficial effects in patients with rheumatoid arthritis (44, 45). In a recent experimental study, investigators found that a soluble p75 TNF receptor fusion protein (etanercept) that binds to TNF and functionally inactivates TNF can reverse some of the cardiotoxic effects of TNF in vitro and in vivo (46). These finding were implemented in a phase I, double-blind clinical trial of patients with NYHA class III heart failure, and it was shown that TNF-α bioactivity was significantly decreased 2 weeks after treatment with a single intravenous infusion of etanercept (Enbrel). Improvements were particularly seen in increased ejection fraction, physical function as measured by a 6-minute walk test, and an overall improvement in quality-of-life scores. Etanercept was found to be safe and well tolerated in this small group of CHF patients (47). However, two large multicenter phase II and III clinical trials, RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) in the United States and RECOVER (Research into Enbrel: Cytokine Antagonism in Ventricular Dysfunction) in Europe, were recently stopped because of a lack of evidence of clinical benefit from etanercept (43).

In another recent study, Sliwa et al. (48) found that pentoxifylline, a platelet antiaggregant that also inhibits its TNF-α production, significantly lowered TNF-α and IL-6 blood levels and improved LV ejection fraction in patients with idiopathic cardiomyopathy after 6 months of treatment. Recently it was demonstrated that intravenous immunoglobulin induced a marked rise in plasma levels of the anti-inflammatory mediators IL-10 and IL-1 receptor antagonist. This changed the balance between inflammatory and anti-inflammatory cytokines that favored an anti-inflammatory net effect in CHF, which significantly correlated with an improvement of LV ejection fraction. Hence, intravenous immunoglobulin has potential for immunomodulating therapy in patients with CHF (49).

DEPRESSION AND CYTOKINES

Major depression is viewed as a disorder that involves abnormalities in the central monoaminergic neurotransmitter system and gives rise to behavioral changes and alterations in neurohormonal pathways. It has recently been suggested that the behavioral deficits, central monoamine abnormalities, and HPA axis

activation observed in major depression are associated with alterations in immune function (50–54).

In 1991 Smith (50) proposed the "macrophage theory of depression." Considering the potent brain effects of proinflammatory cytokines such as IL-1 and the association between pathological states of immune alteration and depression, Smith postulated that excessive secretion of IL-1 and other macrophage products is involved in the pathogenesis of depression. Depression has been associated with immune changes that affect many aspects of the innate immune system, such as 1) impaired zymosan-induced neutrophil phagocytosis (55); 2) mitogen-stimulated lymphocyte proliferation (56); 3) natural killer (NK) cell activity (57); 4) increased numbers of blood lymphocytes, neutrophils, monocytes, and activated T cells; 5) increased serum concentrations of positive acute-phase proteins (C-reactive protein, haptoglobin, α-antitrypsin) and decreased levels of negative acute-phase proteins (albumin, transferrin); and 6) increased secretion of cytokines, particularly IL-6, after in vitro induction by mitogens, particularly IL-1β, IL-6, and interferon gamma (INF-γ) (58).

Cytokines are large (17- to 51-kD) hydrophilic molecules that are unlikely to cross the blood-brain barrier. Four major hypotheses have been proposed for the mechanism by which peripherally released cytokines communicate with the brain: 1) active transport of cytokines across the blood-brain barrier; 2) access of cytokines to the brain in areas where the blood-brain barrier is weak, such as the organum vasculosum of the lamina terminalis; 3) conversion of cytokine signal into secondary signals, such as prostaglandin or nitric oxide signals, by endothelial cells that line the blood vessels of the brain; and 4) transmission of cytokine signals (through cytokine receptor binding) along sensory afferents to the nucleus of the solitary tract and then via ascending catecholaminergic pathways onto the relevant brain regions, including the paraventricular nucleus of the hypothalamus (59).

Although the exact cellular targets of proinflammatory cytokines in the brain are still elusive, it is evident from animal studies that receptors for IL-1, IL-2, IL-6, and TNF-α have been localized in the rodent brain with the highest density in the hippocampus and hypothalamus. In situ hybridization identified the type I IL-1 receptor messenger RNA (mRNA) in several regions of the rat brain, including the anterior olfactory nucleus, medial thalamic nucleus, posterior thalamic nucleus, basolateral amygdaloid nucleus, ventromedial hypothalamus, arcuate nucleus, medial eminence, mesencephalic trigeminal nucleus, motor trigeminal nucleus, facial nucleus, and Purkinje cells of the cerebellum. TNF-α expression and IL-6 expression were documented in human astrocytes and microglia (60). Histochemical studies have revealed that IL-1, IL-6, and TNF-α are expressed in neurons and glial cells within the central nervous system under noninflammatory conditions. After infection or trauma, cytokines are expressed in much larger quantities.

Michael Maes' laboratory has made a major contribution to the understanding that major depression is accompanied by a moderate activation of the inflammatory response system. Some studies have shown increased secretion of IL-6 and IL-8 and increased mitogen-induced production of proinflammatory cytokines such as IL-1β, IL-6, and INF-γ (52, 61, 62). A significant positive correlation was found between cytokine production and acute-phase proteins, which suggests that activation of the inflammatory response system in depression is associated with increased production of the proinflammatory cytokines IL-1β, IL-6, and INF-γ (63). However, these findings have been difficult to replicate. For example, one study reported increases in mitogen-stimulated IL-1β, IL-2, IL-6, IL-10, and INF-α production only during the acute phase of depression (64). Another study reported no increased production of IL-1β and reduced production of IL-2 in major depression. However, the investigators reported that IL-1β was increased in patients with dysthymia and that cytokine alteration was associated with the chronicity of illness and the age at onset (65). Activation of the inflammatory response system involves not only specific immune and metabolic alterations but also neuroendocrine changes, such as hyperactivity of the HPA axis and peripheral and central turnover of 5-hydroxytryptamine (5-HT).

The effects of cytokines on the nervous system and the endocrine system close the loop between the brain and the immune system, which indicates that neural-immune interactions are bidirectional. IL-1 and IL-6 exert potent enhancing effects on the HPA axis by stimulating hypothalamic corticotropin-releasing hormone (CRH), which is capable of activating the neuroendocrine cascade, resulting in increased pituitary adrenocorticotropic hormone and glucocorticoid release (66). CRH is a main regulatory hormone that is secreted in response to stress and that has a wide range of immune functions. For example, CRH has powerful immunosuppressive effect on NK cells and can also inhibit the formation of antibodies such as immunoglobulin G. CRH has also been found to stimulate the release of proinflammatory cytokines in laboratory animals and humans. Administration of CRH in humans leads to an almost four-fold increase of IL-1α and an increase in the immunoregulatory cytokine IL-2. CRH is therefore considered to be capable of exerting immunosuppressive effects on in vivo cellular and hu-

moral responses while having a stimulatory effect on cytokine production and local inflammation (67).

Although studies have shown that both stress and CRH are capable of inducing the production of proinflammatory cytokines in the absence of an antigen-related immune challenge, much remains to be clarified about how immunity is altered in depression. An immune reaction as measured by proinflammatory cytokines is positively correlated with depressive symptoms and with the impaired feedback regulation of the HPA axis in major depression. IL-6 stimulates the HPA axis and exerts its actions on immune cells (66). It has been reported that IL-1β–induced adrenocorticotropic hormone, corticosterone, and IL-6 production is mediated by IL-1 type I receptors (68). Some proinflammatory cytokines, such as IL-1, may induce resistance to the effects of glucocorticoid hormones by influencing glucocorticoid receptor expression or translocation (69).

Proinflammatory cytokines have also been found to have profound effects on the peripheral and brain serotonergic systems. Administration of IL-1β, INF-γ, or TNF-α increases extracellular 5-HT concentrations in several brain areas, such as the hypothalamus, hippocampus, and cortex (70). IL-1β modulates the activity of the 5-HT transporter, which plays a central role in serotonergic neurotransmission by reuptake of 5-HT. Proinflammatory cytokines, such as IL-1 and INF-γ, may induce activity of indoleamine-2,3dioxygenase, which converts tryptophan, a precursor of 5-HT, to kynurenic acid and quinolinic acid. Induction of indoleamine-2,3dioxygenase, which occurs in infection or inflammation, may be detrimental because it leads to depletion of the plasma concentrations of L-tryptophan and reduced synthesis of 5-HT in the brain (71, 72).

Administration of cytokines in humans was found to produce marked behavioral and neuroendocrine symptoms that are similar to those induced by viral infection. Administration of INF-α, IL-2, or TNF-α was found to cause flulike symptoms, such as increased sleep, decreased appetite, and general malaise, as well as depressive symptoms. These symptoms in response to activation of the cytokine network have recently been termed "sickness behavior" (54, 73, 74). In particular, IL-1 has been associated with somnogenic effects. IL-1 has also been associated with learned helplessness, which is an animal model for the cognitive, affective, and motivational aspects of depression (75). Memory and cognitive impairments have been related to IL-2 and in part to TNF-α (76). Administration of IL-2, IL-1β, and TNF-α in animal models was found to cause anhedonia, as evidenced by decreased responding for rewarding hypothalamic self-stimulation and reduced consumption of palatable substances (77). In another study, an injection of *Salmonella abortus equi* endotoxin (a model for host defense activation) caused increases in circulating levels of TNF-α, soluble TNF receptors, IL-6, IL-1 receptor antagonist, and cortisol. Subjects who received the endotoxin showed significant increases in levels of anxiety and depression (78).

Treatment with IL-2 alone or in combination with INFα-2b has been reported to cause neuropsychiatric effects, such as decreased mental performance and in some cases confusion and hallucinatory syndrome, in cancer patients (79). Capuron et al. (80) reported that cancer patients treated with IL-2 immunotherapy developed fever and neurovegetative symptoms in the first week of treatment but did not develop agitation, confusion, or aggressive behavior. In another study they showed that therapy with IL-2 or IL-2 plus INF, in contrast to therapy with INF-α alone, was associated with a significant increase in depression scores early in the course of treatment (81). A recent study reported that cancer patients with depression had markedly higher plasma concentrations of IL-6 than healthy subjects and cancer patients without depression (82). This study indicates that IL-6 also may contribute to sickness behavior that has overlapping symptoms with major depression.

In recent years hepatitis C has been treated with INF-α. This treatment has been associated with a high rate (37%) of interferon-induced depression; in some cases discontinuation of interferon was required (83). Also, treatment of multiple sclerosis with INF-β has been associated with the development of depression (84). In a case series of patients with hepatis C who were treated with INF-α, Gleason and Yates (85) reported that patients with interferon-induced depression responded to antidepressant treatment. This suggests that cytokines are involved in the pathophysiology of some cases of depression and that antidepressants may have an effect on cytokine regulation. This is further supported by another report in which a patient with depression lost the previously good response to paroxetine after being treated with INF-α (86). A recent study by Musselman et al. (87) demonstrated that pretreatment with paroxetine is an effective strategy to minimize INF-α–induced depression in patients with malignant melanoma.

IL-6 is an important mediator of the acute-phase response, and higher levels of acute-phase proteins have been reported in depression (88). Hyperproduction of IL-6 and IL-1β have been associated with the severity of depression; that is, higher serum levels have been found in patients with melancholic depression (63, 89). Other investigators (65) have reported that dysthymia, but not major depression, is associated

with increased production of IL-1β and decreased mitogen-stimulated IL-2 production.

These and other studies indicate a significant heterogeneity of the immunological findings in depression. Zorrilla et al. (90) recently published a meta-analytic review of the relationship of depression and immunological assays. This important study indicates that statistically reliable immunologic differences exist in depressed individuals. Data were analyzed by both the fixed-effects (allows generalization to other subjects) and random-effects approaches (allows generalization to future studies). According to the fixed-effects analysis, major depression was associated with 1) overall leukocytosis, 2) decreases in absolute NK-cell count and relative T-cell levels, 3) increased levels of cells bearing activation markers (CD4/CD8 ratios), 4) increased levels of positive acute-phase proteins and decreased levels of negative acute-phase plasma proteins, and 5) increased serum circulating soluble IL-2 receptor. According to the random-effects analysis, future studies of depressed patients are highly likely to observe 1) lymphopenia and relative neutrophilia; 2) an increased CD4/CD8 ratio; 3) increased levels of circulating haptoglobin, soluble IL-6, and prostaglandin E_2; 4) reduced NK-cell cytotoxicity; and 5) a reduced lymphocyte proliferative response to mitogen. They conclude that major depression may be associated with immune activation reminiscent of an acute-phase response and is reliably associated with impairments in NK- and T-cell–mediated functions.

CYTOKINES AS POTENTIAL THERAPEUTIC TARGETS IN DEPRESSION

Although there is growing interest in understanding the association of cytokines and major depression, an important question is being posed about whether antidepressant treatment is affecting the cytokine system. Animal studies and in vitro work have shown that incubation of monocytes with the antidepressants clomipramine, imipramine, or citalopram produced a marked inhibition of lipopolysaccharide-induced IL1-β, TNF-α, and to a lesser extent IL-6. IL-2 and INF-γ release from T cells was also inhibited by preincubation with these antidepressants (91). In another in vitro study, the effect of clomipramine, sertraline, and trazodone was studied on the stimulated production of INF-γ and IL-10 in whole blood of healthy volunteers. All three antidepressants significantly reduced INF-γ secretion, and clomipramine and sertraline significantly increased IL-10 secretion in the culture supernatant (92). Investigators in an earlier study reported that long-term treatment with the tricyclic antidepressant amitriptyline blocked the lipopolysaccharide-induced febrile response in a dose-dependent manner (93).

Investigators in another experimental study reported that long-term treatment with imipramine, fluvoxamine, and maprotiline produced a profound increase in IL-1ra (the endogenous antagonist of IL-1 receptors) mRNA expression in rat brain (94). This indirectly suggests that antidepressants may alleviate depressive symptoms by inhibiting cytokine secretion from immune cells in vivo or by increasing brain concentration of IL-1ra and thereby blocking the action of IL-1 in the central nervous system.

Cassidy and O'Keane (95) hypothesized that the pathogenesis of depression after treatment with INF-α is related to disturbance of the HPA axis. Exogenous INF-α is believed to have an indirect effect on the HPA axis through activation of endogenous cytokines, specifically IL-6, which is also known to stimulate release of corticotropin-releasing factor from rat hippocampus in vitro. An increased level of serum IL-6 was found to positively correlate with INF-α–induced changes in serum cortisol (96). However, other authors suggest that INF-α reversal of a preexisting antidepressant response is due to the antiserotonergic actions of interferon (86). Another recent study reported that sertraline-treated patients with multiple sclerosis and comorbid depression had significantly reduced production of INF-γ after 16 weeks of treatment (97).

Considering the recent increased interest in depression and immunity, there have been relatively few studies examining the effects of antidepressants on immune function in depressed patients. In addition, the study findings have been somewhat inconsistent. Although some studies have reported one or more immune system parameters being affected by antidepressant treatment, others showed no treatment effect (Table 1). Increased levels of IL-6 observed during an acute depressive episode were normalized after an 8-week period of fluoxetine treatment. However, this process was observed only in one third of 22 patients with major depression (88).

Other investigators reported that a 4-week treatment with clomipramine increased production of IL-1β, IL-3, and IL-2 but showed no correlation between cytokine levels and severity of depression before or after treatment (98). Production of the cytokines IL-6 and TNF-α was assessed in 24 patients with major depression before and after 6 weeks of treatment with amitriptyline. Unstimulated pretreatment production of IL-6 was decreased in responders and increased in nonresponders in comparison with control subjects. This study suggests that secretion of TNF-α is affected by antidepressant treatment or that its level changes with the depression treatment response. It also sug-

TABLE 1. Selected Studies of Antidepressants and the Immune System

Study	Description	Antidepressant	Outcome
Kubera et al., 2001 (102)	In vivo and in vitro treatment	Imipramine, venlafaxine, fluoxetine, L-5-hydroxytryptophan	All increased production of IL-10 and reduced INF-γ/IL-10 ratio.
Lanquillon et al., 2000 (99)	In vivo, 6-week treatment	Amitriptyline	Pretreatment IL-6 decreased, in responders and increased in nonresponders. Posttreatment TNF-α decreased in responders.
Frank et al. 1999 (103)	In vivo and in vitro, 4-week treatment	Fluoxetine (in vivo/in vitro) paroxetine (in vitro only)	Fluoxetine (in vivo) augments NK cell activity only in patients with low levels at baseline. Fluoxetine and paroxetine (in vitro) both augment NK cell activity.
Schleifer et al., 1999 (104)	In vivo, 6-week treatment	Nortriptyline	Initially increased leukocytes and decreased NK cells, T cells, CD4+, CD29+, and CD45RA+. No treatment effect on NK.
Brambilla and Maggioni, 1998 (105)	In vivo, 30-day treatment	Phosphatidyl-serine	No treatment effect on IL-1β, IL-6, TNF-α.
Hinze-Selch et al., 1998 (106)	In vivo, 5-week treatment	Amitriptyline, nortriptyline, paroxetine	Amitriptyline and nortriptyline increased sTNFRp55 and sTNFRp75 but had no effect on TNF-α and sIL-2r. Paroxetine had no effect on TNF.
Ravindran et al., 1998 (107)	In vivo, 12-week treatment	Nefazodone, paroxetine, sertraline, venlafaxine	NK cells initially increased and then normalized in drug responders.
Landmann et al., 1997 (108)	In vivo, 12-week treatment	Moclobemide	No treatment effect on TNF or INF-γ.
Maes et al., 1995 (109)	In vivo, 12+ weeks of treatment	Fluoxetine, tricyclic antidepressants	No treatment effect on IL-6, sIL-6r, sIL-2r transferrin receptor.
Pariante et al., 1995 (110)	In vivo, 12+ weeks of treatment	Desmethylimipramine	NK cells initially increased in depression and decreased with treatment in nonresponders.
Seidel et al., 1995 (64)	In vivo, 6-week treatment	Tricyclic antidepressants	IL-2, IL-10 and INF-γ initially increased and normalized post-treatment.
Sluzewska et al. 1995 (88)	In vivo, 8-week treatment	Fluoxetine	Pretreatment increased IL-6, which normalized with treatment.
Rabkin et al., 1994 (111)	In vivo, HIV/AIDS patients, 6-week treatment	Imipramine	No effect on CD4 count.
Weizman et al., 1994 (98)	In vivo, 4-week treatment	Clomipramine	Decreased IL-1β, IL-2, and IL-3–like activity and increased posttreatment IL-1β and IL-3–like activity.

gests that baseline IL-6 level may be useful in dichotomizing patients into subsequent responder and nonresponder subgroups (99).

CONCLUSIONS AND FUTURE DIRECTIONS

In the last decade there has been rapid expansion of research in cytokine biology. The role of cytokines has been assessed in a variety of medical conditions that traditionally are not considered to have an infectious or inflammatory pathogenesis, such as heart failure and depression. Hence, the theory of cytokine and immunomodulation has led to the question about a possible link between cytokines and the pathophysiology of depression and CHF.

On the basis of available evidence on the role of cytokine in CHF and depression, the following conclusions can be made:

Congestive Heart Failure and Cytokines

- Proinflammatory cytokines exert deleterious effects on the heart. Overproduction of cytokines contributes to the progression of heart failure, and it may be a marker of more severe or more active disease.
- A high plasma level of IL-6 is a powerful independent predictor of mortality. High levels of TNF-α correlate with the severity of symptoms and with mortality.
- sTNFR2 inhibits TNF activity and leads to reversal of the cardiotoxic effects of TNF.

Depression and Cytokines

- Major depression is accompanied by a variety of immunomodulatory processes that affect innate responses of the immune system, including those

of cellular components (macrophages, monocytes, neutrophils, and NK cells) and soluble mediators (acute-phase proteins and cytokines).

- The most consistently increased proinflammatory cytokines in major depression are IL-1β, IL-2, IL-6, INF-α, and INF-γ.
- Treatment with IL-2 and INF-α2b in patients with cancer, INF-α in patients with hepatitis C, and INF-β in those with multiple sclerosis leads to high rates of depression. Some patients respond to antidepressant treatment.
- At present it is inconclusive whether antidepressants have immunoregulatory effects and, if they do, whether they have a direct effect on the immune system or whether their putative immune effects result from improved mood.

Congestive Heart Failure and Depression

There is growing evidence that the prevalence of depression is increased in patients with CHF and that CHF patients with depression have a higher rate of mortality. The underlying mechanism for this comorbidity is unclear. Currently there are no proposed neurobiological or neuroimmune mechanisms for the comorbidity of heart failure and depression. Hence, we propose that the increase of IL-6 in depression may be a mediator of mortality in both CHF and IHD. IL-6 seems to be the most logical pursuit because of its significance in immune regulation and its overlapping involvement in depression and CHF as separate conditions.

This review is in agreement with a recent review by Dantzer et al. (100), who point to evidence of cytokine involvement in major depression. However, there seem to be inconsistencies in the finding of immune regulation markers and the exact role of cytokines in the pathophysiology of depression that need further clarification. According to Dantzer et al., future research would need to clarify the dysregulatory processes that affect neuroendocrine-immune interactions, their contribution to the pathophysiology of depression, and the role of cytokines in the therapeutic effects of antidepressants. Interestingly, according to the Zorrilla et al. meta-analysis (90), some immune markers in depression have been identified as more likely to be found in future studies, which suggests that the use of newer immunoassays may ultimately lead to higher reproducibility of findings.

This review also points to evidence of inconsistency in the findings that relate to the cytokines studied in depression. One reason for the large variation of cytokines in depression and the effects of antidepressants may be that cytokines are involved in many dynamic interactions. For example, simultaneous exposure of cells to multiple cytokines can lead to quantitatively different responses and can therefore result in increased or decreased levels of cytokines, or it can affect production of another cytokine or expression of another cytokine receptor. In addition, the identification of a large number of cytokines is making it difficult to have a clear picture of their role and overlapping of function, that is, their redundancy. Also, it is unclear how we should interpret the findings of the circulating cytokine levels if the connection between the central and peripheral cytokines is done through the signaling role of cytokines. Another complicating factor is that administering exogenous proinflammatory cytokines may be helpful in some cases (eg, INF-α for hepatitis C) and detrimental in others (eg, TNF-α in CHF). Although the therapeutic use of cytokines may be easier to understand, the development of strategies to antagonize pathogenic cytokines is more complex. The cytokines that have been the primary targets as pharmacological agents include the inhibitors of TNF and IL-1.

Clearly the current literature has not yet addressed the role of cytokines in comorbid depression and CHF. Figure 1 depicts cytokines that may be involved in both conditions and that may be a focus of future research if cytokines are considered to be involved in their pathogenesis. From the current literature it is difficult to dissect whether the inflammation is responsible for the depressive symptoms or the depressive state sets the stage for activation of the inflammatory process as it is expressed by elevated cytokines. When considering the relationship between depression and CHF in the context of clinical outcome and the role of cytokines, one can speculate that depression may be only a marker of poor outcome and that

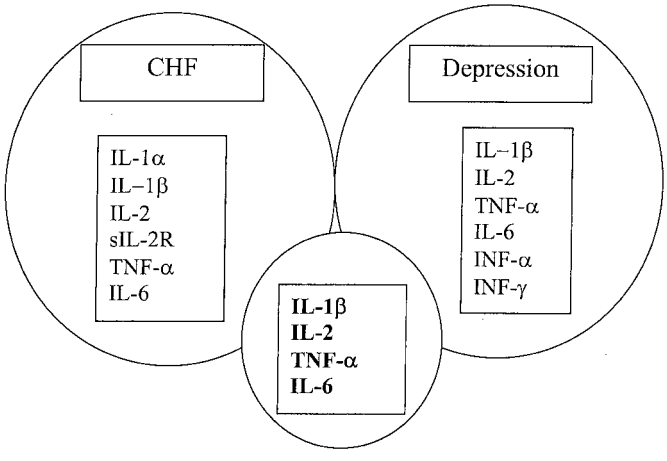

Fig. 1. Overlap of the proinflammatory cytokines involved in CHF and depression.

the pathophysiological mechanism may need to focus on cytokines as common mediators of the comorbidity. One potential explanation could be that both depression and CHF participate in an underlying inflammatory process that is mediated by cytokines. There are several possibilities to be further explored: 1) whether depression could be a marker of inflammation, 2) whether depression fosters inflammation, 3) whether cytokines amplify existing depression, and 4) whether subclinical heart failure leads to depression through cytokine involvement. When considering that cytokines may be involved in increased morbidity and mortality in comorbid depression and CHF, heart failure research targeting treatments with immunomodulatory agents seems to be a step ahead of research on depression. Currently it is unclear whether antidepressants have predictable effects on cytokines in depressed patients. Additionally, at this time there are no reports in the literature on the use of antidepressants in CHF patients with comorbid depression. Drawing from the preliminary results of the Sertraline Anti-Depressant Heart Attack Trial (SADHAT), a trial of sertraline in IHD in which clinical improvement was noticed in >85% of patients, one would expect that a similar trial will be necessary for CHF patients with depression (101).

It is evident from the current literature that cytokines have opened new avenues in the understanding of the integration of diseases and brain-body interaction in depression and heart failure. Future research should focus on 1) whether treatment of depression with antidepressants in patients with comorbid CHF would improve clinical outcomes; 2) clarification of the effects of antidepressant drugs on immune functions, cytokine secretion, and the effects of cytokine synthesis blockers and antagonists in depressive disorders with and without CHF; and 3) whether focusing on the overlapping cytokines involved in CHF and depression (IL-1β, IL-2 TNF-α, and IL-6 in particular) as targets of treatment would improve the outcomes of comorbid CHF and depression. (102–111)

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