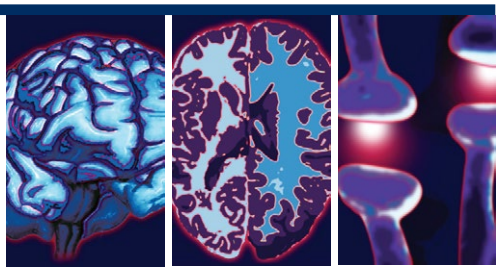
Review



Depression and Inflammation: Disentangling a Clear Yet Complex and Multifaceted Link

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Abstract

While it is unlikely that Major Depressive Disorder (MDD) is a primary and pure 'inflammatory' disease, evidence is accumulating to show that depression and inflammation are closely connected and may fuel each other. Specifically: 1) patients with inflammatory diseases are more likely to show greater rates of MDD; 2) a large number (approximately one-third) of people with major depression show elevated peripheral inflammatory biomarkers, even in the absence of a medical illness, and 3) patients treated with cytokines (i.e. for chronic infective hepatitis) are at increased risk of developing depression. Indeed, inflammatory mediators have been found to alter glutamate and monoamine neurotransmission, glucocorticoid receptor resistance and hippocampal neurogenesis. Also, inflammation is able to alter brain signalling patterns, to affect cognition and to contribute to the production of a pattern of symptoms, clustering in a syndrome named 'sickness behaviour' and closely related to depression. Moreover, it is becoming increasingly clear that inflammation may increase the complexity and severity of illness presentation, as well as treatment response, at least among a subpopulation of individuals with MDD.

Not surprisingly, a number of illnesses, including diabetes, metabolic syndrome, rheumatoid arthritis, asthma, multiple sclerosis, cardiovascular disease, chronic pain, and psoriasis, are characterized by increased risk for depression.

This paper provides a review on the mechanisms by which inflammation may interact with neurotransmitters and neurocircuits to influence the risk for depression. The links between depression and inflammation are analyzed with special reference to the presence of increased inflammatory markers in patients with depression, to the relationship between inflammation and cognitive symptoms of depression, to the relationship between depression and medications that may promote or halt inflammation and to the relationship between depression and certain inflammatory diseases.

Keywords

Depression, Inflammation, Neurotransmitters

Introduction

Several studies have described the link between inflammation and depression [1-7] and the fact that the two conditions are closely connected and may fuel each other in a bidirectional pathway, in which inflammatory responses can lead to depression and depression can lead to inflammation. While it is unlikely that MDD is a pure 'inflammatory' disease, evidence is accumulating to indicate a role for inflammation in the pathophysiology of depression. Most

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of the evidence that connects MDD to inflammation derives from three factors: 1) patients with inflammatory diseases are more likely to show greater rates of MDD; 2) a large number (approximately one-third) of people with major depression show elevated peripheral inflammatory biomarkers, even in the absence of a medical illness, and 3) patients treated with cytokines (i.e. for chronic infective hepatitis) are at increased risk of developing depression. Indeed, inflammatory mediators have been found to alter glutamate and monoamine neurotransmission, glucocorticoid receptor resistance and hippocampal neurogenesis. Moreover, inflammation is able to alter brain signalling patterns, to affect cognition and to contribute to the production of a pattern of symptoms, clustering in a syndrome named 'sickness behaviour' and closely related to depression [8]. Although it is unclear the extent to which inflammation contributes to depression onset and relapse [9-11], it is becoming increasingly clear that inflammation may increase the complexity and severity of illness presentation, as well as treatment response, at least among a subpopulation of individuals with MDD [12]. Although longitudinal studies have shown that elevated serum cytokine levels often precede, and therefore potentially cause depressive symptoms [13,14] , the direction of causality is still being studied and the possibility that depression worsens the course of inflammatory illnesses cannot be ruled out, at least in a subset of patients.

Not surprisingly, a number of illnesses, including diabetes, metabolic syndrome, rheumatoid arthritis, asthma, multiple sclerosis, cardiovascular disease, chronic pain, and psoriasis, are characterized by increased risk for depression [15,16]. For instance, nearly 20% of subjects with cardiovascular disease experience major depressive disease (MDD) [17], patients with diabetes are twice as likely to develop depression [18] and up to 70% of patients with autoimmune diseases, such as systemic lupus erythematosus [19] or rheumatoid arthritis [20] experience depression.

This paper will provide a review on the mechanisms by which inflammation may interact with neurotransmitters and neurocircuits to influence the risk for depression. The links between depression and inflammation will be analyzed with special reference to the presence of increased inflammatory markers in patients with depression, to the relationship between inflammation and cognitive symptoms of depression and between depression and medications that may promote or halt inflammation. The paper will also focus on the relationship between depression and diabetes, rheumatoid arthritis and other inflammatory related diseases, in an attempt to deepen the knowledge into the relationship between depression and inflammation by looking at illnesses that are characterized by an alteration of immunity mechanisms.

Depression and Inflammatory Biomarkers

Several studies have pointed to the presence of increased inflammatory cytokines in subjects with major depressive disorder (MDD). Inflammatory cytokines are cell-signaling protein molecules that are released during inflammation and launch signaling cascades able to activate the immune system. Type 1 cytokines include tumor necrosis factor-α [TNF-α], interferon-γ, interleukin [IL]-1) and serve the primary role of enhancing cellular immune responses. Type 2 cytokines include IL- 6, IL-10, IL-13 and are more linked to antibody responses. These cytokines also prompt acute phase proteins that further activate the immune system, such as C-reactive protein (CRP) [8,21,22].

Proinflammatory cytokines may be either produced in the brain itself or reach the brain from the periphery, through active transport or 'leaky' regions across the blood brain barrier (BBB). Also, cytokines may signal the brain through the afferent vagal pathway or via the entry of activated monocytes into the brain from periphery. Finally, the endothelial lining of the BBB may generate second messenger signals, this leading to an excess production of cytokines by glia [8].

The mechanisms by which inflammatory cytokines modulate the pathways that are implicated in the aetiology of depression is not completely clear but it is becoming increasingly evident that these cytokines can change brain function and structure through mechanisms that are still being studied but may include effects on neurotransmission, for instance via an increase in glutamate induced neurotoxicity, as well as effects on the HPA axis or on hippocampal neurogenesis, [8]. Also, proinflammatory cytokines increase the activity of serotonin transporter (SERT) proteins, resulting in an increase of serotonin reuptake and and in a reduction of extracellular serotonin.

Moreover, proinflammatory cytokines are able to up-regulate enzymes such as tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO), with a resulting decrease in tryptophan (TRP) availability for serotoning synthesis. Finally, quinolinic acid (QUIN) and 3-hydroxykynurenine (3-HK) may elevate the levels of reactive oxygen species (ROS) and oxidative stress within the brain, while QUIN increases N-methyl-D-aspartate (NMDA) activity, resulting in hippocampal atrophy and loss of glucocorticoid receptors and leading to a loss of negative feedback and over-activity in the hypothalamic-pituitary-adrenal (HPA) axis [23].

Human studies have demonstrated that patients with depression exhibit the key features of an inflammatory response, including increased levels of acute-phase reactants, chemokines and soluble adhesion molecules as well as an increased expression of pro-inflammatory cytokines and their receptors, both in peripheral blood and cerebrospinal fluid (CSF) [22,24]. Increased levels of IL-6, IL-8 and type I IFN-induced signalling pathways have been described along with a variety of innate immune genes and proteins, including IL-1β, IL-6, TNF, Toll-like receptor 3 (TLR3) and TLR4 [Miller, 2015]. Indeed, several meta-analyses [1,25,26] have compared patients with MDD and controls and shown differences in proinflammatory cytokines-such as tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), interleukin-6 (IL-6), IL-1β, the soluble IL-2 receptor, and the IL-1 receptor antagonist (IL-1ra). For instance, a meta-analysis of 24 studies measuring cytokines in depressed patients [1], showed that individuals with MDD had significantly higher concentrations of TNF-α and IL-6 compared with controls. Similarly, a meta-analysis of over 50 studies, demonstrated that the majority of researches indicate that depressed patients have shown elevations in the proinflammatory cytokines, interleukin (IL)-6, and IL-1β as well as increased levels of the acute phase protein, C-reactive protein (CRP). Indeed, results from the National Health and Nutrition Examination Survey [27] highlighted that 47% of depressed participants had a CRP level ≥3.0 mg/L, and 29% had a CRP level ≥5.0 mg/L. On the same line, a recent meta-analysis has revealed that tumor necrosis factor (TNF)-α is increased in patients with major depression [25]. Of interest, increased peripheral inflammatory markers have been demonstrated among antidepressant non-responders more often than in treatment responders [28,29].

Cytokine Mediated Cognitive Dysfunction

Patients suffering from depression display a number of cognitive dysfunctions, within the domains of memory, attention and executive function and cognitive deficits have been shown to correlate positively with the levels of proinflammatory cytokines and with the presence of other inflammatory mediators [30]. Indeed, a growing body of preclinical and clinical data suggests that inflammatory changes may well contribute to cognitive changes and that pro-inflammatory cytokines play a central role in synaptic plasticity and other cellular mechanisms that underlie cognition [31].

The relationship between neuroinflammation and cognitive dysfunction is supported by the studies showing an association between markers of inflammation and illnesses such as Parkinson's disease, Alzheimer Disease (AD), and mild cognitive impairment (MCI). For instance, in late-stage AD beta-amyloid plaques are very often co-localized with proinflammatory cytokines, activated microglia, acute phase proteins, and complement factors [32,33].

Neuroinflammation may lead to behavioral and cognitive changes through several mechanisms, including alteration of gene expression, modification in neuronal function, decreased neurogenesis, and impaired long-term potentiation [34]. Of interest, a growing body of evidence points to the possibility of closely linked inflammatory etiology that is shared between depression and cognitive impairment and that may stem from a cytokine-induced imbalance in the kynurenine pathway. This pathway is responsible for tryptophan (TRP) degradation and hence plays a major role in serotonin (5-HT) synthesis and in the key balance between neuroprotective and neurotoxic metabolites. Kynurenine pathway is being looked as a possible target for treatment interventions. However, most of the medications that are presently being used or tested for this purpose are more targeted towards the downstream receptors, enzymes, or transporters than towards the inflammatory basis of such disorders. Other strategies with anti-inflammatory benefits, such as regular physical exercise, may provide an effective intervention for the treatment, prevention or modulation of diseases such as depression or cognitive impairment. Indeed, regular exercise has been recurrently shown to reduce inflammation and to protect against several related disorders [23].

Relationship between Depression and Medications that Promote or Halt Inflammation

Patients receiving interferon-alpha (INF-alpha)- a potent inducer of cytokines- for treating hepatitis C, multiple sclerosis, malignant melanoma, and some blood cancers have higher rates of depression than those not administered interferon [2].

Not surprisingly, changes in monoamine neurotransmitters and along the HPA axis, which mimic those seen in depressed patients, have been described in individuals receiving immunotherapy treatment [3,10,35]. Also, the administration of immunotherapeutic agents, such as the typhoid vaccine, has led to depressive symptoms and to brain changes similar to those observed in MDD [4,35].

There have been few successful trials investigating whether treatment with anti-inflammatory agents can ease depressive symptoms in humans and anti-inflammatory agents such as acetylsalicylic acid (aspirin), cyclooxygenase-2 (COX-2) inhibitors, and TNF receptor antagonists have shown the ability to improve depression treatment [35]. For instance, meta-analyses of randomised controlled trials (RCTs) of non-steroidal anti-inflammatory drugs (NSAIDs), given in monotherapy or as adjunct to antidepressants, indicate that these medications may be more effective than placebo in treating depression [36,37]. Although these results confirm an inflammatory component of depression, the extent to which the antidepressant effect of NSAIDs may be exclusively attributed to their anti-inflammatory action is unclear. In fact, NSAIDs effects may be due to an activity on other targets, such as glucocorticoid receptors [38].

Moreover, given that many trials of NSAIDs medications for depression are based on patients with chronic physical diseases, it is difficult to establish how much of the improvement in depression is attributable to an improvement in the main physical disorder.

Studying the antidepressant effects of cytokine modulators, i.e. monoclonal antibodies and cytokine inhibitors, may provide a model that is easier to understand. A recent proof-of-concept RCT of the tumor necrosis factor alpha (TNF-α) monoclonal antibody infliximab, showed improvements in patients with treatment-resistant depression and high inflammation at baseline [6].

Also, greater remission of depressive symptoms with the TNF-α antagonist infliximab were seen in Crohn's disease patients [39], while TNF-α antagonists have shown efficacy in patients with depression within the context of autoimmune disorders or other conditions with increased inflammation [40,41]. A systematic review and meta-analysis of antidepressant efficacy of anti-cytokine treatment was recently conducted using clinical trials of chronic inflammatory conditions where depressive symptoms were measured. A significant antidepressant effect of anti-cytokine treatment compared with placebo was showed and anti-TNF drugs were most commonly studied. Statistically significant improvements in depressive symptoms were observed for adalimumab, etanercept, infliximab and tocilizumab and the antidepressant effect was associated with baseline symptom severity but not with improvement in primary physical illness, sex, age or study duration. This finding confirm a potentially causal role for cytokines in depression and indicates the possibility that cytokine modulators may be developed and used as novel drugs for depression, at least in subjects with chronic inflammation.

However, inflammation is neither sufficient nor necessary to induce and/or to sustain depression and vice-versa. Hence, a clinical benefit from anti-inflammatory agents may only occur in the subset of depressed patients with heightened inflammation [9]. For instance, Raison and colleagues evaluated 60 patients with treatment-resistant depression (TRD), in a double-blind, placebo-controlled, randomized clinical trial, to determine if the inhibition of the inflammatory cytokine tumor necrosis factor (TNF) can reduce depressive symptoms and if treatment response may be predicted by an increase in baseline plasma inflammatory biomarkers, including C-reactive protein (high sensitivity-CRP), TNF, and its soluble receptors. Study subjects received an infusion of infliximab, a TNF antagonist administered at 5 mg/kg (n = 30) or placebo (n = 30) at baseline and weeks 2 and 6 of a 12-week trial. Interestingly, infliximab did not show a generalized efficacy in TRD. Yet, it showed the ability to improve depression in those subjects with higher baseline hs-CRP concentration. In fact, 62% (8 of 13 subjects) of study participants with a baseline hs-CRP concentration greater than 5 mg/L showed a response (defined as ≥50% reduction in HAM-D score at any point during treatment) to infliximab versus only 3 out of the 9 patients (33%) with high baseline

hs-CRP that had been assigned to placebo treatment. Similarly, among patients treated with infliximab, baseline levels of TNF and its soluble receptors were significantly higher in responder's *vs* non-responders [6].

Similarly, Rapaport and colleagues evaluated a group of 155 patients with major depressive disorder (MDD), to establish if inflammatory biomarkers such as interleukin (IL)-1ra, IL-6, high-sensitivity C-reactive protein (hs-CRP), leptin and adiponectin, act as moderators of clinical response to omega-3 (n-3) fatty acids.

Study subjects were randomized to treatment with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or placebo. Interestingly, subjects with high levels of inflammation markers improved more on EPA than placebo and the separation between EPA and placebo increased with increasing numbers of markers of high inflammation [42].

Depression in Patients with Other Medical Illnesses Related to Inflammation

Inflammation plays a role in the pathogenesis of several neurological, metabolic and behavioral diseases including depression, dementia, and metabolic disorders. Conversely, these disorders have been shown to contribute to the elevated inflammatory state, this resulting in a vicious cycle [23]. Several mechanisms may explain this relationship. In addition to the ability of inflammatory cytokines to directly impact the nervous system cytokines may directly stimulate receptors within the hypothalamic-pituitary-adrenal (HPA) axis, with the result of influencing hormone secretion. Moreover, several cytokines may indirectly influence endocrinal and neurological disorders by an interference with the regulation of enzymes, which may determine a shift in key metabolic pathways, with resulting imbalance in critical neuroactive molecules [23].

Depression in Diabetic Patients

Comorbid depression and diabetes is a challenging and under-recognized clinical problem, despite the fact that a relationship between depression and diabetes has been recognized for a long time [43-45]. Given the high prevalence of diabetes and depression, a degree of comorbidity is to be expected. However, epidemiological studies have consistently demonstrated that the 2 diseases occur together twice as frequently as would be expected by chance alone [18,46]. Moreover, several studies in various medical and psychiatric settings have shown that depression is associated with hyperglycemia and higher rates of diabetes related complications and that relief of depression is associated with improved glycemic control [18, 47,48].

For instance, Anderson and colleagues conducted a metanalysis to estimate the rate of depression in individuals with type 1 or type 2 diabetes and found that the odds of depression in subjects with diabetes were twice that of the non-diabetic comparison group. The prevalence of comorbid depression was significantly higher in diabetic women (28%) than in diabetic men (18%) but the presence of diabetes doubled the odds of comorbid depression in both genders.

A meta-analysis of 9 cohort studies reported a 37 % increased risk of developing type 2 diabetes in adults with depression [18] after accounting for shared factors including sex, body mass index, and poverty. However, a considerable heterogeneity across studies was reported, with the association risk varying from a non-significant increased relative risk of 1.03 to a very significant risk of 2.50. A further meta-analysis of 13 studies reported that incident depression in subjects with diabetes at baseline was more likely by 15 % (OR 1.15 (95 % CI 1.02–1.30) [49].

Negative correlations of depression in patients with diabetes include poorer adherence to treatment [50], increased risk of vascular complications (eg, neuropathy, macrovascular complications, diabetic retinopathy) [51], worsened control of glycemia [50], and poor metabolic control [52]. Also, in patients with diabetes depression tends to last longer and is associated with decreased quality of life and increased disability [53], more somatic symptoms [54], increased health care costs and higher mortality risk [52,55].

A number of epidemiologic studies have shown that the correlations between depression and diabetes is bi-directional [49,56]. Yet, the meaning of depression in the context of diabetes is not straightforward and several models have been suggested to explain the comorbidity of depression and diabetes. For instance, depression can be a comprehensible reaction to the problems resulting from a challenging and life-shortening chronic medical illness and to its related complications. Moreover, lifestyle factors and behavioural habits related to depression may contribute to the correlation with diabetes. For instance, people with depression are more likely

to be physically inactive, eat diets that are rich in saturated fats and refined sugars while reducing the intake of fruit and vegetables, have an increased body mass index and not adhere with weight loss recommendations, which may well increase the risk of developing type 2 diabetes [57-59].

In addition to the psychosocial models mentioned above, the co-occurrence of diabetes and depression is likely fueled by common pathogenic mechanisms. In other words, the co-occurrence may be driven by shared underlying biological mechanisms, such as hypothalamic-pituitary-adrenal axis activation, inflammation, alterations of the sympatho-adrenal axis [60], and increased proinflammatory cytokines [61], which may contribute to insulin resistance, diabetes risk and depression [45,47].

For instance, a dysfunction of the hypothalamic-pituitary adrenal (HPA) axis, may manifests as subclinical hypercortisolism, blunted diurnal cortisol rhythm, or hypocortisolism with impaired glucocorticoid sensitivity, and increased depression and inflammation [45,62].

Chronic inflammation may also stand alone to underlie the correlation between depression and diabetes, as inflammatory cytokines and markers, such as TNF-α, C-reactive protein, and other proinflammatory cytokines, are increased in diabetes, in the metabolic syndrome and in a portion of subjects with depression. Not surprisingly, those markers have shown the ability to cause depression in human beings and sickness behavior in animal models, with symptoms that include negative mood, anhedonia, increased pain sensitivity, fatigue. loss of appetite, and cognitive deficits, a cluster of symptoms that well remind human depression [45,60,63].

Depression, Rheumatoid Arthritis and other Inflammatory Related Diseases

Several Inflammatory diseases have been associated with elevated rates and a greater severity of depression presentation. Depression occurs 5-10 times more frequently among those with a medical illness, worsening their prognosis and disability, especially when the illness is linked with an autoimmune process. For instance, the rate of MDD in multiple sclerosis reaches 50%, with a suicide rate as high as 15% [64,65]. This occurrence is not limited to inflammatory disease that interest CNS, being seen also in peripheral inflammatory diseases such as rheumatoid arthritis (RA), psoriasis and inflammatory bowel diseases, which show rates of MDD that are conservatively estimated between 13% and 17% [8,20,65,66], with some studies reporting an even higher prevalence. For instance, a recent review of 17 studies involving patients with systemic lupus erythematosus (SLE) reported prevalence rates of depressive disorders, within the range 17–75% [67]. As in similar inflammatory illnesses, depression may result from the psychosocial impact of a chronic disease as well as from lesions of the central or peripheral nervous system owing to cytokines induced biochemical and neurophysiological changes. For instance, in patients with SLE, cytokines may cause or sustain depression via activation of the indoleamine 2,3-dioxygenase (IDO) enzyme as well as through the alteration of neurotransmitters' bioavailability, the modification of neurogenesis and neuroplasticity and via the overstimulation of certain neural circuits. Furthermore, cerebro-reactive autoantibodies present in the cerebrospinal fluid (CSF) of patients with SLE, such as anti-N-methyl-D-aspartate (NMDA) and anti-ribosomal P, may damage neurons in brain areas that are relevant to mood and behavior, thus causing depressive symptoms [68].

In patients with rheumatoid arthritis (RA), prevalence estimates for depression have widely ranged across studies, with results ranging from 9.5% [69] to 41.5% [70], depending on the study methodology and on the chosen threshold for depression. For instance, a study by Robinson and colleagues involving 144 patients with rheumatoid arthritis, stated that almost 60% of the female patients and 35% of the males reported to have felt depressed at some time [71]. In a systematic review and meta-analysis on the prevalence of depression in RA, Matcham and colleagues included a total of 72 studies, with more than 13 000 patients, and reported that 43 methods had been used to define depression. The authors reported differences across multiple studies, mainly depending on the definition of depression and on the threshold that was used for the diagnosis of depression. The overall prevalence of major depressive disorder (MDD) resulted 16.8%, whereas the Patient Health Questionnaire (PHQ-9) prevalence of depression was 38.8%, and the prevalence levels according to the Hospital Anxiety and Depression Scale (HADS), with thresholds of 8 and 11 were 34.2% and 14.8%, respectively. Despite the differences among the single studies, it is clear that these rates are significantly higher

than the prevalence rates observed in the general population [72] and are comparable to, or higher than, those reported in subjects with diabetes [73], Parkinson's disease [74] and cancer [75].

Hence, it is clear that both depression [72,76-79] and depressive symptoms [80,81] are common in persons rheumatoid arthritis (RA). These conditions have been correlated with reduced quality of life [82], increased pain [83], fatigue [84], increased degree of physical disability [85], increased health care costs [86], more comorbidities [87] and increased mortality levels [88]. Depression should therefore be a useful target for interventions aimed at improving subjective health and quality of life in RA patients, as well as in individuals with other inflammatory diseases.

As for the other illnesses described above, the relationship between RA and depression may be mediated by several factors. For instance, emotional responses to a physical illness characterized by pain and debility may play an important role. Also, somatic symptoms that are common in RA (e.g. poor sleep, loss of appetite) are also common, and shared with, depression.

As in other illnesses previously described, pathogenesis of RA seems to be multifactorial and involve key pro-inflammatory cytokines such as IL-1 and TNFα. However, recent discoveries have pointed to a role of novel cytokines, including IL-17, IL-18 and RANK ligand (RANKL) and confirmed that inflammation and tissue damage are the outcome of multifaceted cell-cell interactions in the rheumatoid synovium [89,90].

Nonetheless, it is clear that a dysregulation in the cytokine network plays a crucial role in the pathogenesis of RA and likely contribute to its association with depression. TNF and IL-1 are among the most studied cytokines and are considered to play a key role in the process of chronic joint inflammation and erosive cartilage and bone changes that are seen in RA. These observations are consistent with the fact that anticytokine treatments have proven clinical efficacy, especially with approaches directed against tumor necrosis factor (TNF)-alpha. Proinflammatory cytokines may contribute to the development of MDD in multiple ways, including their effects on the HPA axis, on neurotransmission and possibly a direct action on hippocampal neurogenesis.

However, RA is primarily considered a 'peripheral disease' and the role of cytokines in causing depression during illnesses that primarily affect the brain (eg, depression during multiple sclerosis or post-stroke depression) is more easily understood than their role in peripheral illnesses. Peripheral immune activation, such as that seen with RA, but also with local infections or injuries, is followed by release of cytokines such as IL-1α , IL-1β , IL-6, and TNF-α. However, these cytokines are not small enough to freely pass through the blood-brain barrier (BBB). Yet, it is now known that the brain itself is able to produce cytokines and that peripheral cytokines can signal the brain through several ways, such as a passage through certain cytokines permeable regions in the BBB, through active transport across the BBB, through the afferent vagal, or through an excess production of cytokines by glia induced by second messenger signals from the endothelial lining of the BBB.

Regardless of the exact mechanisms that are involved, it is clear that inflammatory mediators, whether they are generated peripherally or centrally by specific diseases or they are given exogenously (as with IFN therapy) can lead to depression and that a significant subset of individuals with depression show an increase of inflammatory factors, such as IL-6, TNF-α, and CRP, even when they are not diagnosed with an inflammatory disease.

Although the mechanisms that have been described as potential mediators of the relationship between depression and inflammatory illnesses likely represent only a few of the many causal paths, they potentially explain many features of a complex relationship and provide help to design newer studies for a deeper understanding of the pathophysiology of depression and of certain inflammatory diseases, with the ultimate goal to develop better intervention strategies.

Conclusions

Inflammation plays an increasingly evident role in the pathogenesis of a number of immune system, neurological and behavioral disorders, including depression, cognitive impairment, metabolic and autoimmune diseases.

Clearly, depression, diabetes and inflammatory illnesses are linked in several ways, although neither appears to be absolutely necessary or sufficient for the other. However, there is a significant subset of patients for whom inflammation may precipitate or prolong depression or for whom depression may significantly contribute to the inflammatory

response, course and outcome of the comorbid disease.

As the role of inflammation is becoming increasingly appreciated for a growing number of diseases, treatments aimed at restoring a balance of the immune system and its inflammatory mediators should be considered as a potential strategy of treatment and prevention. A new group of anti-inflammatory drugs may help treat depression and the link between these drugs and depression may shed further light on the role that inflammation plays in depression.

More studies are needed to explore the relationship between depression and inflammation, possibly stemming from an evaluation of the relationship between depression and illnesses such as diabetes, rheumatoid arthritis and other inflammatory illnesses. Those studies may lead to a better understanding of the pathogenesis of each single disease and of the mechanisms that mediate or moderate the co-occurrence. In the meantime, a treatment model that incorporates assessment and treatment of both comorbid conditions seems necessary for improved outcomes.

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