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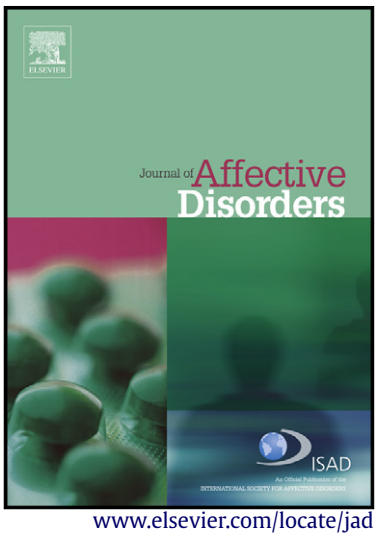

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A Review of the Relationship between Proinflammatory Cytokines and Major Depressive Disorder

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Abstract

Background:

Determining etiological factors and reviewing advances in diagnostic modalities sensitive and specific to Major Depressive Disorder (MDD) is of importance in its evaluation and treatment. The inflammatory hypothesis is one of the most prevalent topics concerning MDD and may provide insight into the pathogenesis of depression, development of biomarkers, and ultimately production of more effective depression therapies.

Method:

We reviewed several studies to evaluate contemporary concepts concerning proinflammatory cytokines and their relationship to various depressive disorders, the use of anti-inflammatory therapies in MDD treatment, and the application of neuroimaging in conjunction with cytokine profiles from both plasma and CSF as possible diagnostic tools.

Results:

Proinflammatory cytokines in both plasma and CSF have been found to influence the progression and severity of depressive disorders in different populations. Studies have shown elevated serum levels of IL-1, IL-6, TNF-α, CRP, and MCP-1 in depressed patients, but have presented mixed results with IL-8 serum levels, and with IL-6 and MCP-1 CSF levels. Anti-inflammatory treatment of MDD may have adjuvant properties with current depression medications. MRI and NIRS neuroimaging confirm neurological abnormalities in the presence of elevated proinflammatory cytokines in depressed or stressed patients.

Limitations:

Heterogeneity of MDD and limited CSF cytokine research complicate the study of MDD pathogenesis.

Conclusion:

There is significant evidence that inflammatory processes influence the development and progression of MDD. Future studies with larger arrays of cytokine profiles aided by neuroimaging may provide more sensitive and specific modes of diagnostics in determining MDD etiology and provide guidance in individual therapies.

Keywords:

Inflammatory hypothesis, proinflammatory cytokines, immune activation, major depressive disorder, neuroimaging.

Introduction

Major depressive disorder (MDD) is a public health concern, with high lifetime prevalence (16.2% among US adults), differing levels of symptomatic severity, and potential for significant impairments in daily functions (Kessler et al., 2003), therefore making the identification of its causes a research priority. Critically, research into the etiology of MDD needs to take into account the heterogeneous nature of the illness, and requires the development of methods by which to characterize and assess objectively severity of depression, response to treatment, and to classify MDD into its different subtypes (Schmidt et al., 2011). In this respect, central nervous system (CNS) inflammation has been suggested to play a significant role in MDD pathogenesis due to findings of increased proinflammatory cytokines levels in patients with neurodegeneration and symptoms of depression such as anhedonia, depressed mood, and lethargy (Miller et al., 2009). Moreover, studies have also shown elevated plasma levels of proinflammatory cytokines in diagnosed MDD patients who had attempted suicide, with suicidal ideation, and geriatric depression suggesting that inflammatory mechanisms may be positively associated with different subsets of depressive disorders (Miller et al., 2006; O'Donavan et al., 2013; Sublette et al., 2011). The objective of this review is to discuss concisely the current evidence for the "inflammation hypothesis" in depression, and to determine the possibilities of proinflammatory cytokine diagnostics in identifying and describing depressive disorders.

The Inflammatory Process and Hypothesis in MDD

Although it is unclear how cytokines may initiate or influence the pathogenesis of depressive disorders, one hypothesis postulates that proinflammatory cytokines stimulate indoleamine 2,3-dioxygenase (IDO) in glial cells to convert tryptophan to kynurenine which is transformed into the neurotoxic quinolinic acid inside the brain (Müller and Schwarz, 2007;

Walker et al., 2014). Quinolinic acid binds to N-methyl-D-aspartate receptors while also depleting tryptophan leading to a decrease in overall serotonin levels and an increase in glutamatergic activity commonly associated with depression (Sublette et al., 2011). This is believed to be the biochemical mechanism of neuronal damage and loss of neuronal plasticity that leads to an increase in suicide attempts among a subgroup of MDD patients with elevated plasma kynurenine levels (Sublette et al., 2011), although other studies have suggested that increased kynurenine levels without a decrease in tryptophan levels could also lead to depressive-like behavior in both animal models and human subjects (Raison et al., 2010). A number of animal studies also support the association of inflammatory states with depressive symptoms, decreased hippocampal volumes, and "sickness behavior" (Goshen et al., 2008; Goshen and Yirmiya, 2009; Lawson et al., 2013).

It is therefore unsurprising that an association between proinflammatory cytokines and MDD has been reported in a number of studies. Individuals with depressive symptoms, including MDD patients, have shown elevated plasma levels of proinflammatory biomarkers, including IL-1, IL-6, TNF-α, and C-reactive protein (CRP) compared to healthy controls (Azar and Mercer, 2013; Miller et al., 2013; Thomas et al., 2005). For example, a cross-sectional study of 49 individuals diagnosed with MDD, but no other significant medical disorder or substance abuse, found that approximately 75% of the subjects demonstrated relatively higher levels of nine proinflammatory cytokines (Simon et al, 2008). Furthermore, patients with SSRI-resistant depression were shown to have higher IL-6 and TNF-α levels compared to normal controls, and formerly SSRI-resistant patients (O'Brien et al., 2007).

The central and peripheral immune systems maintain a homeostasis of proinflammatory and anti-inflammatory signaling proteins to allow both systems a medium by which they

communicate rapidly with one another to alter brain biochemical properties when responding to peripheral stimuli (Merrill and Jonakait, 1995). The peripheral immune system is characterized by the processing of immunogenic pathogens and activation of neutrophils and macrophages resulting in the release of cytokines that signals the microglia-dominated central immune system. The central immune system then responds to the peripheral cytokines through upregulation of proinflammatory proteins, receptors, and hormones within the CNS (Morimoto and Alexopoulos, 2011). Dysregulation of this system is thought to lead to the structural and biochemical changes associated with MDD development.

The peripheral cytokines are produced as a result of phagocytic cells expressing Toll-like receptors (TLRs) recognizing pathogen-associated molecular patterns (PAMPs) (Barton and Kagan, 2009). One commonly studied PAMP is lipopolysaccharide (LPS) endotoxin, a component of gram-negative bacterial cell walls that elicit a significant immune response in a number of organisms. LPS is recognized by and binds to TLR4, thereby inducing the production of proinflammatory cytokines IL-1α and IL-1β (Barton and Kagan, 2009; Dantzer, 2006). In turn, these cytokines stimulate the production or potentiate the action of other proinflammatory cytokines such as TNF-α and IL-6 produced by antigen-presenting cells. Once these cytokines are able to influence the CNS, they exert an effect on the HPA axis, promoting fever, decreased food intake, and excessive release of corticotrophin release hormone (CRH), thus leading to the disruption of the negative feedback loop to the HPA axis and the promotion of glucocorticoid resistance within the immune system (Dantzer, 2006). This process is believed to be a possible etiologic factor in the development of long-term inflammatory states in chronic depression (Sapolsky et al., 1986). A review of cytokine-induced alterations in neuroplasticity has suggested that HPA axis hyperfunction is linked to a reduction of hippocampal volumes, impaired neuronal

plasticity, and decreased neurochemical functioning resulting in depressive symptoms (Hayley et al., 2005). In addition to the HPA pathway, the sympathetic nervous system activated by the same initial inflammatory signaling processes leads to a release of norepinephrine into the peripheral tissues causing β-adrenergic receptor stimulation and further upregulation of IL-1, TNF, and IL-6 (Slavich and Irwin, 2014).

Importantly, cytokines cannot enter the CNS directly through the blood-brain-barrier (BBB) due to their relatively large size and their hydrophilic properties. It has been speculated that peripheral cytokines enter the CNS via access through more permeable regions such as circumventricular organs and the organum vasculosum of the lamina terminalis (OVLT). Proinflammatory cytokines such as TNF-α and IL-1β have been found to affect the CNS in this way, but typically only in high levels that influence central immune behavior through receptor-induced cascade reactions rather than the more locally-oriented immune responses found in the periphery (Woodroofe, 1995). A review of BBB transport of cytokines indicated that this is more likely due to the presence of saturable active transporters associated with the cytokines IL-1, IL-6, and TNF-α rather than a diffusion gradient across the BBB (Banks, 2005). Interestingly, researchers (Saris et al, 1988) have shown that IL-2, a cytokine that is typically not found in the CNS, could be present in the CSF in persistent disease states such as those found in cancer patients, suggesting that the BBB may become compromised during similar diseased states thus allowing peripheral cytokine access into the central immune system. Alternatively, non-physiologic conditions may cause an upregulation of transporters throughout the BBB thus allowing the elevation of cytokine levels in the CSF.

In addition to these pathways, neural transmission has also been found to promote inflammatory changes within the CNS. The vagal nerve afferents are known to have a major role

in the development of acute immune responses to immunogenic foreign agents (Maier and Watkins, 1998). It has been postulated that the expression of IL-1 receptors in vagal sensory neurons and the presence of perineural sheath macrophages and dendritic cells within vagal branches mediate the neural transmission during inflammation (Banks, 2005). Studies in mice have indicated that vagotomy decreased response to pain, fever, and glucocorticoid levels while also resulting in less sickness behavior (Maier and Watkins, 1998). One study demonstrated attenuated behavioral depression in mice that underwent a vagotomy compared to mice with sham surgical procedures (Konsman et al., 2000). Another study also described attenuated LPS-induced depression-like symptoms in mice that underwent subdiaphragmatic vagotomy (Layé et al., 1995). However, these findings are not always confirmed. A recent study showed that complete vagotomy in mice that displayed depression-like behavior after interferon-α (IFN-α) treatment did not lead to a decrease in such behavior (Friebe et al., 2013). Analogously, a study of vagal nerve stimulation in chronic MDD patients only showed a positive response in approximately 1/3 of the cases of chronic unipolar depression refractory to antidepressant treatment (Christmas et al., 2013). Finally, other studies have reported vagal anti-inflammatory influences on the immune system suggesting multiple functions of vagal innervation, and highlighting the heterogeneity of mechanisms affecting CNS immune behavior (Christmas et al., 2013; Friebe et al., 2013; Raison et al., 2006).

A review (Frick et al., 2013) detailing studies concerning cytokine effects on different immune cells indicated that data on microglial dysregulation are “limited” and reported mixed results relating to increased microglial densities and activation in diagnosed MDD patients in both clinical and post-mortem examinations. However, the review also found that aggregated animal studies commonly implicated microglial activation with depressive phenotypes in rats

that undergo chronic psychological stress, neonatal LPS injection, and mice with CX3CR1 (fractalkine receptor) deficiencies. Although activation of microglial cells is a likely mechanism by which inflammation is propagated as a result of peripheral signaling, further research pertaining to human microglial studies in response to immune signaling is needed in order to understand the specific processes and effects that microglial activation has on depressive and sickness syndromes.

Effects of Anti-inflammatory Medications on Depression

If the inflammatory hypothesis of depression is correct, then anti-inflammatory medications (e.g., nonsteroidal anti-inflammatory drugs, NSAIDs) can be used, either directly or indirectly, to decrease depressive symptoms, especially for the 30-40% cases that are treatment-resistant (Kornstein and Schneider, 2001). Recently, several studies have provided tentative evidence in support of the effectiveness of therapeutic interventions based on a reduction of inflammation, although more research is still needed.

Interactions between antidepressant medications and inflammatory signaling pathways have been suggested in a recent review (McNamara and Lotrich, 2012), although with caution due to inconsistent results. Irregularities could be due to the diverse effects on proinflammatory cytokine production caused by different antidepressant formulations. For example, in an *in vitro* investigation of citalopram, mirtazapine, and escitalopram stimulation of cytokine production, researchers have shown that Citalopram and Mirtazapine increased inflammatory cytokine production, whereas escitalopram administration decreased cytokine concentrations (Munzer et al., 2013). Critically, escitalopram,but not the other drugs, decreased recurrence of MDEs, suggesting that the efficacy of antidepressant medications may depend upon reduction of inflammatory cytokine secretion.

A randomized controlled trial demonstrated that TNF antagonism with Infliximab was found to exhibit efficacy in TRD patients with hs-CRP concentrations greater than 5mg/L (Raison et al., 2013). However, when observing for Infliximab efficacy in comparison to placebo treatment in patients with lower inflammatory biomarker levels, Infliximab use had significantly worse efficacy suggesting that only the subset of patients with elevated hs-CRP concentrations were likely to respond to cytokine antagonism. In addition, TNF antagonism had no significant effect on study participants as a whole when not accounting for inflammatory biomarkers. These results are further supported by a study that demonstrated similar effects of Infliximab on mildly stressed rats including decreased depression and anxiety-like behavior when compared to controls and saline administration (Karson et al., 2013). All in all, these findings raise the possibility of TRD populations who could be uniquely responsive to anti-inflammatory intervention, thus suggesting the need for appropriate screenings and treatment.

Studies have reported that adding NSAIDs to SSRI therapy decreases severity of depression, as measured with the Hamilton Depression Scale, implying increases in antidepressant effects (Akhondzadeh et al., 2009; Müller, 2013). These studies suggest an adjuvant role for NSAIDs in TRD treatment. In contrast, a large scale randomized controlled trial designed to evaluate NSAID treatment (celecoxib & naproxen) in approximately 2,500 elderly adults with late-life depression found no significant effect in reducing modified Geriatric Depression Scale (GDS) scores compared to placebo (Fields et al., 2012), suggesting that anti-inflammatory monotherapy may be insufficient to produce significant antidepressant effects. Further studies are necessary to characterize efficacy based on different NSAID dosages and combined use with different antidepressant medications.

MCP-1 and IL-8 in Depression

Chemokines are proteins with chemoattractant properties that act as mediators of the immune-inflammatory reaction and regulate leukocyte infiltration into the brain parenchyma during disease states (Banisadr et al., 2005). As such, they are necessary in the propagation of inflammation and subsequent increase in proinflammatory cytokine production in the CNS. Two of the more commonly studied chemokines in depression include monocyte chemoattractant protein-1 (MCP-1/CCL2) and IL-8. MCP-1 is a known chemokine that induces leukocyte infiltration and neuronal damage during CNS inflammation and has been associated with neurodegeneration in multiple sclerosis, Alzheimer's disease, brain ischemia, and trauma (Banisadr et al., 2005). For these reasons, MCP-1 has been investigated for its possible role in affecting inflammation and MDD. One study has reported overexpression of MCP-1 to be associated with the severity of depressive symptoms in healthy male subjects with low to moderate levels of depression (Suarez et al., 2003), while another study found elevated levels of MCP-1 in MDD-diagnosed patients with no other known comorbidities (Simon et al, 2008).

IL-8, on the other hand, is a known neutrophil chemokine that has a central role in the recruitment and infiltration of neutrophils into inflammatory sites during acute inflammation and has been implicated in depressive episodes (Harada et al., 1994). Suarez and colleagues (Suarez et al., 2003; Suarez et al., 2004) have conducted two studies that demonstrated increased IL-8 plasma levels in depressed subjects. In one study, they demonstrated that increased severity of depressive symptoms was correlated with increased levels of plasma IL-8 (Suarez et al., 2003). In another study, they showed that severity of depression was associated with LPS-induced increased serum IL-8 concentration (Suarez et al., 2004). In contrast, however, another study has shown serum MCP-1 and IL-8 concentrations to be lower in MDD diagnosed subjects of a Finnish population as compared to controls (Lehto et al., 2010). This study also found that only

MDD subjects that were prescribed antipsychotic medications showed an increase in IL-8 serum levels. It may be therefore possible that the plasma IL-8 chemokine is primarily elevated in the acute inflammatory stages, and does not play a significant role in the chronic inflammatory pathogenesis of MDD. This conjecture would account for the fluctuations in serum IL-8 levels within different studies. Therefore, plasma IL-8 may be a less accurate chemokine biomarker for chronic depressive disorders as opposed to MCP-1.

CSF Cytokines and Chemokines in Depression

Although a large body of research has been dedicated to finding links between plasma proinflammatory cytokine levels and depressive disorders, there are fewer studies concerned with studying cerebrospinal fluid (CSF) cytokine levels and depression. This scarcity is mainly due to the relative difficulty of obtaining CSF samples, higher costs and perceived level of discomfort. Nevertheless, current results are promising and show altered levels of proinflammatory biomarkers in CSF samples of depressed patients relative to healthy controls (Raison et al., 2010).

One of the first studies of CSF biomarkers looked at IL-1β, IL-6, and TNF-α levels in a small group of unmedicated, acutely depressed patients (Levine et al., 1999). This study found higher levels of IL-1β and decreased levels of IL-6 in the CSF of depressed patients compared to healthy controls while there was no significant difference of CSF TNF-α between the two groups. These findings are consistent with observed decreased levels of IL-6 and its soluble receptor in the CSF of geriatric patients with major depression (Stübner et al., 1999). However, in contrast, one study showed a positive correlation between CSF IL-6 levels and depressive symptoms, and suicidal behavior (Lindqvist et al., 2009), whereas another study of patients with unipolar MDD determined that there were no differences in IL-6 levels between healthy controls

and depressed patients (Carpenter et al., 2004). Finally, a longitudinal study of older women over a decade of intermittent psychiatric evaluations showed that low CSF IL-6 concentrations predicted the emergence of depressive symptoms (Kern et al., 2013). The inconsistency in the results may be attributable to the differences in cytokine gene expression in response to an acute inflammatory stimulus versus a chronic one, or may be the result of different depressive etiologic factors on IL-6 production. Additionally, IL-6 is one of the few proinflammatory cytokines to also have anti-inflammatory effects (Slavich and Irwin et al., 2014), thus suggesting that the increase or decrease in IL-6 concentrations may not always parallel the production of other proinflammatory cytokines during inflammatory states. These findings blur the exact role of IL-6 in the pathogenesis of MDD and indicate that IL-6 interactions with neuronal and immune cells should be further explored.

As discussed previously, several studies have found plasma MCP-1 to be associated with inflammatory processes and depression severity. However, this review was able to find only one article showing significantly elevated CSF MCP-1 levels in subjects with depression. In this study, patients given IFN-α, a treatment known for eliciting negative symptoms such as depressed mood, anxiety, lack of motivation, changes in sleeping habits, and deficits in memory, were reported to have increased concentrations of CSF MCP-1 compared to healthy controls (Raison et al., 2009). Other studies presented either mixed results (Lindqvist et al., 2011) or lower CSF MCP-1 levels in more severe MDD cases (Gotlib and Hamilton, 2008). Although MCP-1 is regarded as a significant inflammatory biomarker that could be used to characterize MDD subtypes, current literature is not clear on the correlation between CSF MCP-1 and MDD.

Neuroimaging of Depression and Cytokine Concentrations

Considering the high level of comorbidity and difficult differential diagnosis for cases with MDD, the imperative to develop reliable diagnostic tools to evaluate MDD is high. There is significant evidence that anatomical disturbances in the neural structures involved in experiencing and processing emotion predispose individuals to the development of negative symptoms and impair emotional regulation (Gotlib and Hamilton, 2008). Genetic risk factors also appear to influence the development of depression as demonstrated by studies that show healthy patients with a positive family history of depression being more likely to have decreased hippocampal and dorsolateral prefrontal cortex (DLPFC) volumes compared to a control group with no family history (Amico et al., 2011). Additionally, in the same study, MDD subjects also exhibited decreased anterior cingulated cortex, dorsomedial prefrontal cortex (DMPFC), and basal ganglia volumes, suggesting that depressive symptoms may be associated with mesolimbic structural abnormalities. Consistently, the majority of neuroimaging studies in depression are indicative of limbic involvement along with abnormal cortical functioning, but the increase or decrease in activity of individual structures vary according to the closeness of depressive episodes and type of treatment (or lack thereof) (Gotlib and Hamilton, 2008). As with individual cytokines and chemokines, most current neuroimaging biomarkers are neither sensitive nor specific enough to be used broadly to diagnose across a heterogeneous group of disorders, but their study is a necessity in further determining the specific mechanisms of cortical and limbic structures' involvement in MDD. A promising neuroimaging tool that may aid differential diagnosis of MDD from other disorders, such as bipolar disorder and schizophrenia, is the multi-channel near-infrared spectroscopy (NIRS). NIRS can measure haemoglobin concentration changes in the immediate cortical surface areas non-invasively, without interfering with

cognitive or brain processes, and a multi-site case control study has shown it can be used to discern unipolar MDD patients from non-MDD disorders in a clinical setting, though limitations in its low spatial resolution are noted (Takizawa et al., 2014).

Less prevalent are studies dedicated to the observation of brain parenchyma disruption in relation to increases in proinflammatory cytokine levels. A number of MRI studies have shown an association between peripheral inflammatory markers and anomalous brain structure activity. Structural MRI studies demonstrated smaller hippocampal volumes and decreased glucocorticoid activation in MDD diagnosed patients (Frodl and Amico, 2014). In addition, fMRI studies found increased serum proinflammatory cytokine concentrations correlated with increased activity of the subgenual anterior cingulated cortex (sACC) (Harrison et al., 2009), dorsal anterior cingulate cortex (dACC), and anterior insula (Slavich et al., 2010).

While these results have demonstrated structural changes as a result of inflammation in the brain, none of the MRI or fMRI studies described included results concerning cytokine levels in the CSF. Additionally, with the exception of the structural MRI study, these neuroimaging results did not involve diagnosed MDD patients but healthy volunteers that participated in stress-inducing tasks to invoke proinflammatory states. Though these studies indicate a relationship between high proinflammatory cytokine concentrations with structural and functional abnormalities in the brain, they do not definitively demonstrate a causal role of proinflammatory protein expression in the progression of MDD pathology.

Limitations

Although the studies described in this review have demonstrated a relationship between proinflammatory cytokines and depression, no research known to the authors has found cytokines that are highly sensitive or specific to MDD. Additionally, as different studies tend to

concentrate on different cytokines and/or subtypes of MDD, the reported findings concerning cytokine-induced depression can be difficult to replicate or reproduce. A relatively smaller number of studies focusing on CSF inflammatory cytokines also limit the ability of researchers to evaluate the pathogenesis of MDD or determine etiology.

Conclusions

The majority of studies involved in characterizing the inflammatory processes in depression and its associated disorders have yielded mixed and, at times, contradicting results in determining the cause of cytokine-induced depressive states. The heterogeneity of the disease complicates the task, even though a significant amount of literature points to an immunologic reason to depression pathology. Yet, more studies are necessary in order to further characterize the various subsets of depression since a generalized approach to the MDD inflammation hypothesis is an impossible task without more sensitive and specific diagnostic tools available. Future studies involving comparative groups of subsets of MDD diagnosed subjects against healthy controls and the use of larger arrays of proinflammatory biomarkers rather than relying on a small number of cytokines are necessary in more precisely determining the functional relationship between immunogenic alterations in the cortical parenchymal structures and behavioral changes. This is especially true of studies pertaining to cytokine infiltration in the CSF as this review has not been able to find studies that corroborate increased or decreased inflammatory CSF cytokines and functional abnormalities in the brain using neuroimaging modalities. What is required now are novel methods by which to classify MDD subtypes that will hopefully provide a more direct approach in the treatment and management of a diverse population of depressed patients. Obtaining CSF inflammatory profiles in conjunction with

current and future neuroimaging diagnostics is one of the more promising steps in accurately diagnosing depressive disorders.

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Conflict of Interest

The authors do not claim any conflict of interest.

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