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Recent insights into the association of chronic inflammatory and neurodegenerative processes in clinical depression

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Abstract: The aim of this present article is to underscore the recent evidence linking clinical depression to increased inflammatory drive and its significance in development of newer antidepressants. For this purpose extensive bibliographic search of articles were conducted from different referred journals and indexing services such as Pubmed central and Medline. The mechanisms for the underlying association are based on a review of a total of 20 preclinical and clinical literatures on the subject. The literature reviewed suggests that there is substantial evidence of inflammatory and neurodegenerative (I&ND) processes playing an important role in depression and that enhanced neurodegeneration in depression may be caused by inflammatory processes. One hypothesis of depression states that stress leads to the up regulation of multiple pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α (gene factors of NF-kB) The data from preliminary findings in patients with inflammatory disorders suggest that inhibiting pro-inflammatory cytokines or their signaling pathways may actually improve depressed mood and increase treatment response to conventional antidepressant medication. Implications of these findings include reconsideration of dosage regimens of existing antidepressants, and utilization of this knowledge in ensuring future targeted drug development in this area with the aim of ensuring rational therapy for depressive disorders. This review stresses on the fact that even though current understanding of depression is that it is not characterized as an inflammatory condition, inflammation can cause depression and inflammatory cytokines and neurodegenerative pathways are clearly factors which may be modulated for targeted deugs for ameliorating clinically depressive disorders.

Keywords: Chronic inflammation, depression, neurodegeneration, cytokin

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Introduction

Depression is currently seen as a major health problem with the World Health Organization in 2001 predicting that depression is on course to become the second most common cause of morbidity worldwide serving as the basis to study its pathophysiology. Current understanding identifies depression as a group of disorders which has sparked the idea that there may be several neurobiological pathways leading to the disorder. Our article focuses on one such connection linking depression to inflammatory and neurodegenerative processes. Recently it has been established that all risk factors of clinical depressive disorders like disturbances in sleep, stress and trauma leads to the increase in inflammatory processes. The present review is an attempt to find the causality and levels of association to ascertain current understanding of the role of inflammatory and neurodegeneratory (I&ND) processes associated in clinical depression[1].

Over the years, evidence has accumulated to suggest that chronic low grade inflammation plays a significant role in the etiology of major depression. The inflammatory hypothesis (also known as the macrophage hypothesis) of depression was suggested by Smith in 1991 and was further elucidated by a number of researchers [1,2]. The hypothesis is based on the following observations: Pro-inflammatory cytokines (for example, IL-1β, IL-6, interferon-gamma, tumor necrosis factor) are raised in the serum of depressed patients, while anti-inflammatory cytokines, such as IL-4 and IL-10 and omega-3 fatty acids, are reduced.

The pro-inflammatory cytokines can initiate depressive-like behaviour when released from macrophages and microglia by bacterial mitogens or when administered therapeutically for the treatment of hepatitis or some forms of leukemia (e.g: interferon-α). These pro-inflammatory cytokines activate the hypothalamus pituitary adrenal (HPA) axis and thereby contribute to the hypercortisolaemia, a marker of major depression that contributes to the metabolic changes associated with the disorder [2]. By increasing the activity of the tryptophan-kynurenine pathway, pro-inflammatory cytokines reduce brain serotonin synthesis and increase the synthesis of neurotoxins that contribute to the neurodegenerative changes that have been detected in the frontal cortex and many limbic regions of patients with major depression [3]. The therapeutic response to the treatment of depression is correlated with a reduction in pro-inflammatory cytokines.

In addition to these inflammation associated changes, it is now apparent that oxidative and nitrosative pathways are also increased in depression and contribute to the neurodegenerative changes by damaging neuronal membranes and mitochondrial integrity. Thus it becomes apparent that the inflammatory hypothesis links the psychopathology of depression with the medical illnesses that are often co-morbid with the disorder [4-6].

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2. Study Methodology

Comprehensive bibliographic search of published articles on this subject during the last 5 years (2008-2013) were conducted from different referred journals and indexing services such as Pubmed central and Medline. Subsequently the articles were reviewed and the findings were carefully noted. A total of 20 preclinical and clinical literatures on the subject were studied from leading journals from the concerned field and were comprehensively researched to come to the findings.

From the literature studied for the present review it was inferred that the elevated pro-inflammatory cytokines have been proposed as a possible physiological link common to depression and have varying levels based on the seriousness of the medical condition. This increased level of cytokines induce oxygen radical damage with the production of a chemokine, indoleamine 2, 3 dioxygenase (IDO) thereby leading to the formation of tryptophan catabolites and serotonin. This activation of inflammatory pathways within the brain is believed to contribute to a host of events such as decreased neurogenesis and enhanced neurodegeneration. Preclinical studies have also indicated that stress induce the up regulation of the pro-inflammatory cytokine and its expression in parts of the brain [6,7].

As sought the evidence for a link between depression and inflammatory processes is further supported by the fact that pro-inflammatory cytokines (notably IL-2, IL-6, IL-1β and TNF-α) are elevated not only in medically ill patients with depression but also in medically healthy but depressed patients. The degree of elevation of certain pro-inflammatory cytokines has also been shown to correlate with the severity of depressive illnesses. Further evidence has suggested that activation of the systemic inflammatory process (as measured by systemic C-reactive protein) may facilitate current understanding of the pathophysiology of depression.

3. Examining the Depression- Inflammation Connection

Inflammation is a normal physiological process that plays a major role in almost every major medical illness. In each illness inflammation causes the release of cytokines, which behave as chemical messengers and signal cells to the immune system. Presently a large proportion of researchers working in this subject believe a clear correlation between inflammation, neurodegenerative processes and depression. Although the correlative link between depression and inflammation has been identified, the actual mechanism at work remains unclear till date. The inflammatory and neurodegenerative (I&ND) pathways in depression remain a critical element linking inflammation to depression and its clinical manifestations. The key findings in depression are the increased levels of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, interferon-γ, with a relative shortage in the anti-inflammatory cytokine, IL-10 [7,8].

4. Prospects of Targeting Inflammation to treat Clinical Depression

Prior studies have suggested that depressed people with evidence of high inflammation are less likely to respond to traditional treatments for the disorder, including anti-depressant medications and psychotherapy. This study was designed to see whether blocking inflammation would be a useful treatment for either a wide range of people with difficult-to-treat depression or only those with high levels of inflammation [9-11].

One such clinical study employed infliximab, one of the new biologic drugs used to treat autoimmune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. A biologic drug copies the effects of substances naturally made by the body's immune system. In this case, the drug was an antibody that blocks tumor necrosis factor (TNF), a key molecule in inflammation that has been shown to be elevated in some depressed individuals. Study participants all had major depression and were moderately resistant to conventional antidepressant treatment[12]. Each participant was assigned either to infliximab or to a non-active placebo treatment. Findings from the study indicated no significant differences were found in the improvement of depression symptoms between the drug and placebo groups. However, when the subjects with high inflammation were examined separately, they exhibited a much better response to infliximab than to placebo. Inflammation in this study was measured using as C-reactive protein or CRP test. The higher the CRP, the higher was the inflammation and the higher the likelihood of responding to the drug [13-16].

5. Conclusions

While depression is not an inflammatory condition, inflammation can cause depression, and inflammatory cytokines are clearly a factor. This idea has profound implications in neuropsychiatry and medicine. It suggests that inflammatory processes will be highly relevant to some individuals with depression, irrelevant to others, and perhaps even of benefit to a minority of depressed individuals. Recent data suggest that the widely available blood test for C-reactive protein may identify individuals with greater or lesser likelihood of responding to anti-inflammatory therapeutic strategies and, by extension, individuals for whom inflammation is more or less of a causative factor. Such identification of patients with depression and increased inflammation represents a critical first step to the personalization of care, allowing specific treatments to be directed to specific pathologies that can then be monitored as a function of response.

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