Inflammation and Depression

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INTRODUCTION

Depression is increasingly recognized as a major health problem and World Health Organisationhas predicted that by the year 2020, depression will be the second most common cause of morbidity worldwide.[1] The pathophysiology of depressive disorder is very complex as there are multiple etiological factors operating in an interactive fashion to make the person vulnerable to depressive episodes.This article attempts to explore the link between depression and inflammatory processes.

The link between inflammation and depression was noted from the studies 'sickness behaviourand depression' and 'the macrophage theory of depression.' Association between chronic immune activation in medical disorders with an inflammatory pathophysiologyand depression; immunotherapy for cancer and hepatitis C and ageing was explored.[2-4]Recently, there are many studies reporting that other risk factors for depression such as psychosocial stress, psychosocial trauma, sleep disturbances and pain increase inflammatory processes.

IMMUNOTHERAPY AND DEPRESSION

It has been observed 30-45% of patients receiving alpha interferon develop depression as a side effects.[3]A higher rate of psychiatric illness exists in patients with hepatitis C than in general population which may be due to the side effects of alpha interferon administration or direct neurotoxicity of the hepatitis c virus itself. However, interferon treatment used for other diseases including malignant melanoma also causes neuropsychiatric side effects. Thus, where a pro-inflammatory cytokine is used to treat a disease, it also appears to directly cause a depressive illness in a significant proportion.

Mechanismunderlying inflammation and depression : There are several mechanisms which have been suggested to explain the link between inflammation and depression.

Direct action of cytokines on the brain : Cytokines administered exogenously to treat illness such as hepatitis C can cause neuropsychiatric side effects which provides evidence that cytokines can directly affect the brain.[4]The raised pro-inflammatory cytokines profile observed in depression suggests that the raised cytokines levels may be producing symptoms by exerting a direct effect on the brain, particularly hypothalamus.[5]Similarly Wann also hypothesizes that pro-inflammatory cytokines is responsible for initiating changes in the amygdala.[6]

Effects on the immune system : Depression is associated with elevated levels of corticotrophin-releasing hormone(CRH) in the central nervous system (CNS). In vitro studies have suggested that central doses of CRH can decrease both cellular and humoral immune responses as well as natural killer cell activity which therefore illustrate one possible mechanism by which depression can induce the immunosuppression. Increased levels of circulating catecholaminesand neuropeptides Y is found in people with depression. These seem to have strong predictive value regarding decline of natural killer cells response.[7]

More recent research in this field was performed in the context of depression induced by alpha interferon which shows that mood and cognitive symptoms were highly responsive to pre-treatment with paroxetine whereas neuro-vegetative syndrome (decrease appetite, sleep disturbances, motor retardation) did not respond to antidepressants.[7] This suggests that there may be different pathophysiological mechanisms causing the affective and cognitive symptoms according to the effects on the immune system.

Cytokines and the HPA axis : Some patients with depression exhibits hyperactivity of hypothalamic – pituitary –adrenal axis characterised by hypercortisoleamia. Pro-inflammatory cytokines are activators of the HPA axis and there is evidence that persistently raised pro-inflammatory cytokines levels counteract the normal negative feedback loop where by raised corticosteroid levels would reduce HPA axis activity. Raised cortisol is also associated with increased anxiety and fear behaviour and with decreased ability to manage social stress.[8]Aconsistent finding is that cytokines which mediate innate immune responses also increase the release of CRH.

Increased CRH is a reliable finding in major depressive disorders as evidenced by increased cerebrospinal fluid concentrations of the hormone and increased CRH mRNA and protein in post-mortem studies of the hypothalamus of individuals who has had depression. Clinical evidence in support of this is based on the lack of suppression of plasma cortisol following the administration of 1mg of the synthetic glucocorticoid dexamethasone;which is the basis of dexamethasone suppression test (DST), a test that was one time believed to be a biological marker of major depression.[9]

It has been further suggested that cytokine induced activation of the HPA axis may represent a risk factor for depression.Lastly, inflammatory cytokines have been shown to alter nearly all aspects of glucocorticoid receptor functioning and the signal transduction pathways by which cytokines affect glucocorticoid receptors.

Effects of inflammation on neurogenesis : There is evidence that hippocampal volume is reduced in depression so that hippocampal functions including recall are impaired in major depression. Pre-clinical studies suggest that interleukin 1b can impair neurogenesis. In exploring a potential mechanism underlying depression induced by alpha interferon treatment, there was drug supressed neurogenesis in the dentate and interleukin 1b played an essential role in that suppression.[10]

The anti-inflammation activity of antidepressant : There is growing evidence to suggest that commonly used antidepressantdrugs also show anti-inflammatory properties. In vivo animal study suggests thatantidepressants are able to suppress production of interferon-gamma (IFN-γ) independent of their effects on monoamine blockade. Other studies also have suggested similar effects regarding other pro-inflammatory cytokines including tumour necrosis factor alpha (TNF-α). This strongly suggests that antidepressants can act to normalise the mechanism responsible for increased cytokine production.[11]

A hypothesis is that in depression it is the interplay between the HPA axis and the cytokine system that is disturbed. It is suggested that HPA axis activity in acute depression suppresses cytokine regulatory mechanisms and successful antidepressant treatment normalises this relationship.[11]There is also evidence that non pharmaceutical treatment for depression exerts an effect on the immune system i.e. anti-cytokine effect.[12]

The antidepressant effect of anti-cytokine

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treatment : The association between adverse emotional states and rheumatoid arthritis do exists and studies found that prevalence of depression is increased in a population of patients with rheumatoid arthritis.[13] The drug used for the treatment of rheumatoid arthritis and psoriasis has been shown to relieve both the symptoms of psoriasis and depression and fatigue associated with it.[14] Antidepressants have been found to reversed major depression induced by cytokine therapy.[15] Study also showed that the antidepressant exhibit a major rapid onset of action if augmented with aspirin.[16]

CONCLUSION

Although there is little evidence that anti-inflammatory drug is effective as monotherapy for depression, there is evidence that etanercept [an anti-TNF drug] has a hedonic effect. Pre-clinical work implies that other anti-cytokine treatments may reduce the effects of psychosocial stressors.[4]There is much stronger evidence that the existing anti-depressant drugs also possesses anti-inflammatory properties. Both clinical and preclinical studies have shown that antidepressant can reduce levels of pro-inflammatory cytokines. Understanding the relationship between depression and somatic disease can beuseful in patient care. Simply realising that depression is far more likely to occur if patient is physically or medically ill, especially in the context of certain diseases, can help early identification and management. Thus, there is strong evidence that there exist a linkbetween inflammation and depression.

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