Stress, Inflammation and Mental Illness

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Stress causes maladaptive changes in the neurotransmitter, immune and endocrine systems which play a major role in initiating ill-health and major psychiatric disorders. In recent years there has been a paradigm shift in our understanding of the inter-relationship between the hypothalamic-pituitary-adrenal [HPA] and the immune axes. Thus activation, rather than suppression, of important aspects of the immune system occurs following chronic stress. One of the reasons for this is ascribed to the glucocorticoids induced apoptosis of hippocampal neurons that occurs as a consequence of the desensitisation of central and peripheral glucocorticoids receptors. Thus chronic low grade inflammation, which results from the stress induced activation of peripheral and central inflammatory pathways, is central to the pathogenesis of depression and schizophrenia and linked to diabetes, cancer, asthma, arthritis and cardiovascular disease that are frequently co-morbid with these disorders.

Evidence in support of the inflammation hypothesis of major psychiatric disorders was first provided by Smith [Med.Hypoth. 35,298-306, 1991] who suggested that the symptoms of psychiatric disorders arise from the stress and genetically programmed activation of peripheral [macrophages/monocytes] and central [microglia,
Abstract

Astrocytes and oligodendroglia/macrophages that result in the elevation of pro-inflammatory cytokines and other inflammatory mediators, such as prostaglandin E2, in the blood and cerebrospinal fluid. Thus there is an imbalance between the pro- and anti-inflammatory arms of the immune system which characterises most major psychiatric disorders, changes that are largely attenuated following effective treatment.

The rise in glucocorticoids and pro-inflammatory cytokines also results in the activation of the tryptophan-kynurenine pathway whereby tryptophan is shunted away from serotonin synthesis to the formation of kynurenine and its end-products following the activation of indoleamine 2, 3-dioxygenase, by pro-inflammatory cytokines, and tryptophan dioxygenase, by glucocorticoids, respectively. These changes link stress and inflammation with the formation of the neurotoxic metabolites of the tryptophan-kynurenine pathway [3-hydroxykynurenine and quinolinic acid]. Further, in the brain the pro-inflammatory cytokines activate cyclo-oxygenase and nitric oxide synthase thereby increasing the PGE2 and NO concentrations in the brain. These add to the inflammatory stress within the brain [Leonard and Myint, Neurotox.Res. 10,149-160,2006].

This in chronic depression and schizophrenia the inflammatory changes, coupled with stress-induced hypercortisolaemia which blocks the synthesis of neurotrophic factors that normally repair damaged neurons, the neurodegenerative pathways predominate over the neuroprotective pathways, Thus it is hypothesised that chronic stress and inflammation are causally associated with the pathology of major psychiatric disorders such as depression and schizophrenia.