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Oxidative stress: a potential link between emotional wellbeing and immune response

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Emotional wellbeing is central to normal health and good living. Persistent psychological stress often disrupts emotional wellbeing and triggers onset of neuropsychiatric ailments. An integrated, multisystemic stress response involving neuroinflammatory, neuroendocrine and metabolic cascades seem to have some causative links. Of particular interest are the neuroinflammatory processes. Psychological stress has been suggested to negatively affect normal functioning of the immune system contributing to the pathophysiology of some neuropsychiatric conditions. Thus examination of the interaction between the immune system and the central nervous system is likely to reveal molecular targets critical for development of potential therapeutic and preventive measures. This review is a summarized discussion of evidence linking impact of psychological stress on the immune system, with a particular emphasis on oxidative stress mechanisms by which mental stress potentially impacts immune function leading to activation of multiple cascades resulting in subsequent manifestation of psychiatric symptomologies.

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Introduction

Stressful situations often spark varied range of emotions and behaviors including anxiety, irritability, sadness, violence and anger. In most cases, these are temporary responses that disappear once one is out of the situation that caused it but these emotions and behaviors often stay in some when faced with persistent or chronic stress. In fact, persistent psychological stress is well known to adversely impact our overall emotional wellbeing [1]. Both pre-clinical and clinical data have provided novel insights in this regard. Although the link between psychological stress and mental illnesses is strong, yet, the neurobiological mechanisms governing stress-induced deterioration in mental health remain unclear. The association between psychological stress and the immune system is an interesting one and has been a subject of inquiry for quite some time [reviewed in 2], with postulated occurrences of complex interplay between the periphery and the central nervous system (CNS) [3–5].

Theories suggesting involvement of neural, physiologic, molecular, and genomic mechanisms in psychological stress driven psychiatric pathologies have been postulated over the years. In addition to contemporary theories is the hypothesis that oxidative stress triggers the onset of inflammation [6]. Both pre-clinical and clinical data has provided novel insights. Here, we discuss selected pre-clinical and clinical data highlighting the CNS-immune system cross talk. Finally, we offer an interesting hypothesis suggesting oxidative stress as the biochemical trigger for initiating the CNS-immune system cross talk, potentially critical to emotional wellbeing.

Psychological stress, psychiatric disorders and inflammation

Chronic psychological stress and mental illnesses especially major depressive disorder (MDD) are believed to be associated with decreased adaptive/acquired immunity and activation of inflammation [7,8•,9•,10,11•,12,13]. And, it is believed that psychological stress not only increases the risk for depression, but also raises inflammatory cytokine levels [14,15]. In fact, stress in humans can transcriptionally regulate inflammatory cytokine genes [16]. Conversely, elevated cytokine levels are reportedly normalized with antidepressant treatment [17–20]. Basic science research as well as clinical evidence has suggested that social stressors up-regulate proinflammatory cytokine activity, and that proinflammatory cytokines signal the CNS to induce neuro-behavioral alterations presenting with hallmark psychiatric symptoms. This knowledge has initiated an elucidation of neural systems involved in processing how stress is perceived within the brain, converted into physiological and biochemical processes to enable cross-talk between the CNS and the periphery to induce specific symptoms. A greater role of cytokines has emerged from a variety of studies suggesting more than associative links, and a postulation of the immune-based model of depression or cytokine model of depression, has emerged. Key findings are discussed below.

Increased pro-inflammatory cytokines were detected in depressed and anxious patients [21,22••,23•,24,25,26•,

27–29]. And, exogenous administration of cytokines triggered depressive symptoms in human subjects. In fact, a dose–response relationship between interferon-alpha (IFN-α) administration and depression was observed, with a tapering baseline effect on mood following discontinuation [30–36]. And, mood deterioration was reported with endotoxin injections and with inflammatory cytokine vaccines [37,38]. Interestingly, depressed patients when subjected to Trier Social Stress Test, a psychological stress paradigm, showed increased markers of peripheral inflammation, including plasma interleukin-6 (IL-6) and nuclear factor kappa B (NF-κB) DNA-binding when compared to controls. Furthermore, T-helper1 and T-helper2 cytokine imbalance was reported in post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) patients, increasing IL-6 (secreted by Th2 cells) and tumor necrosis factor alpha (TNF)-α (necessary for the induction of Th2 responses) concentrations [39]. It is suggested that deficits in serotonergic activity may be related to decrease in Th1 cytokines with a shift toward Th2, which most likely gives rise to anxious symptoms. Decreased T-cell proliferation was found in anxious patients compared to controls and the production of Th1 cytokines, IL-2 and IFN-γ and Th2 cytokines, IL-4 and IL-5, following T-cell activation was lower [40]. In addition, anti-inflammatory IL-10 was lower in anxious patients. Significant increases in Th1 cytokines, TNF-α and IL-17, are also associated with generalized anxiety disorder (GAD) patients [40], supporting the role of the immune system in this disorder. Alterations in C-reactive protein (CRP) levels have also been exhibited in patients diagnosed with GAD [41].

Role of elevated plasma cytokines has also been proposed in autism spectrum disorders, and inflammation has been associated with stereotypy in autism [42]. Bipolar disorder patients are reported to exhibit increased plasma pro-inflammatory cytokine levels, including interleukin-IL-6 and tumor necrosis factor-α. Furthermore, increased levels of IL-1β, NKκB and IL-1RA protein and mRNA were noted in frontal cortex tissues of bipolar patients [43]. Also, increased levels of acute phase protein haptoglobin and CRP; and higher complement factor concentrations of plasma C3C or C4 have been reported to be associated with bipolar disorder patients [44]. Post-mortem studies have revealed that inflammation-related genes are differentially transcribed in the brains of depressed subjects, and that genetic variability in the inflammatory system genes may be associated with depression [45]. Some have even suggested that persistent psychological stress creates a 'transcriptional fingerprint' on peripheral monocytes exhibited with increased pro-inflammatory gene expression, particularly related to the NF-κB pathway [46,47]. The 'transcriptional fingerprint' of stress on monocytes is postulated to be linked to an exaggerated pro-inflammatory responses and subdued anti-inflammatory defenses. Thus there seems to be broad support that inflammatory cytokines are key elements in the pathogenesis of depression as well as other mental illnesses. Animal models, as discussed below, have provided important insight and support to the immune model of psychiatric disorders.

Animal research has suggested that, inflammatory cytokines can influence behaviors that are homologous to depression. Various stress models have demonstrated stress-induced behavioral impairment along with activation of inflammatory cytokines [48,49] and subsequent suppression of neurogenesis and neuroplasticity mechanisms. Gárate *et al.* [50] demonstrated that repeated restraint stress from stressful acoustic exposures upregulate TLR-4 pathway suggesting an important role for TLR-4 in neuroinflammation. These results support TLR-4 as an important regulatory factor in the stress response system and an attractive pharmacological tool to minimize inflammatory damage in the brain upon stress. Using a modified model of predatory stress (PS), Barnum *et al.* [51] reported that psychological stress in adolescent and adult mice increases neuroinflammation and attenuates lipopolysaccharide (LPS)-induced behavioral deficits.

Psychological stress, inflammation, oxidative stress and psychiatric disorders

Enhanced pro-inflammatory cytokine signaling may promote generation of reactive oxygen species (ROS) and lead to oxidative damage. Thus oxidative stress might be one mechanism that links inflammation to psychological stress and neuropsychiatric diseases. This hypothesis seems feasible considering the following mechanistic information. Stress-induced excitotoxicity releases the excitatory amino acid, glutamate, in the brain [52], which induces the release of pro-inflammatory cytokines such as TNF-α. Stress also activates the inflammatory NFκB pathway through a TNF-α-dependent mechanism. NFκB is a transcription factor, known to be activated by ROS, cytokines and glutamate, and thought to be a mediator of oxidative stress in neurodegenerative processes and also considered to be responsible for the induction of pro-inflammatory cytokines. And, NF-κB activation regulates the expression and activity of pro-inflammatory enzymes, such as the inducible NOS (NOS-2) and COX-2. The result of this sequel is the accumulation of oxidative and nitrosative mediators, which alter membrane phospholipids and causing cell damage by lipid peroxidation [53]. This has been observed in the brain after exposure to stress.

Inflammatory and oxidative and nitrosative processes may also affect antioxidant defense system which act to neutralize oxidative stress. This system comprises of a glutathione (GSH) system. GSH system includes glutathione peroxidase (GPx) and glutathione reductase (GLR)