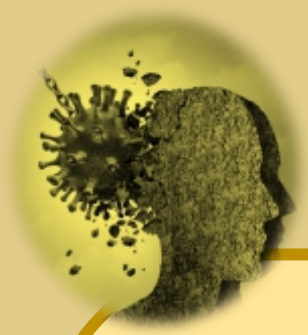

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REVIEW ARTICLE

Immune-inflammatory Pathways in Somatoform-Disorders : A Theoretical Update

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ABSTRACT

Somatoform disorders are comprised of conditions where patients have multiple somatic symptoms without any underlying medical explanation for the causation of such symptoms and cause significant psychosocial distress. These somatic complaints often occur in major depression and chronic fatigue syndrome where involvement of immune-inflammatory pathways has been described, which suggests their possible involvement in somatoform disorders. This stimulated research and lead to unravelling the possible role of mechanistic pathways like cell-mediated immunity and subsequent inflammation, the involvement of TRYCAT (tryptophan catabolite), and oxidative/nitrosative stress pathways in somatoform disorders. In this review, we attempt to provide an overview of the three possible pathways elucidated to date as a precise understanding of the biological underpinnings has profound implications in stimulating further research in these poorly understood group of disorders.

Keywords: somatoform disorders, somatization, inflammation, immunity, autoimmunity

INTRODUCTION

Nearly a decade ago, Rief and others published their pioneering work documenting the relationship between the inflammatory response system and somatization and comparing it with major depression. While they found some evidence for immune-inflammatory system activation in somatization syndrome, they also found key differences in activation patterns; patient with somatoform disorder showed decreased concentration of CD8 + T-lymphocytes and IL-6 and raised levels of some anti-infammatory markers (Clara cell protien CC-16) [1]. These changes are relatively stable over time. [2]

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Subsequently, a credible body of evidence has established common biological underpinnings between depression, somatization, and specific symptom syndromes such as chronic fatigue syndrome.[3–5] This has led to some authors rechristening the term psychosomatic disorder as a "physio-somatic" disorder.[6] These observations are strengthened by clinical observations of frequent co-morbidity and symptom overlap between depression and somatoform disorders; the common underpinning mechanism here may be immune-inflammatory challenges and perturbations.[1]

Traditionally, the origins of somatoform disorder have been attributed to a combination of cognitive and environmental factors; these include adverse childhood experiences [7], and cognitive misinterpretation or catastrophizing of symptoms.[8] However, it is increasingly becoming clear that physiological aberrations may drive, or at least augment, the non-specific symptoms in somatoform disorders. Insights from cognitive neural

science such as somatosensory amplification and psycho-neuroimmunological perspectives are now recognized as key to answering questions such as why some people develop unexplained somatic symptoms and why some 'amplify' or 'catastrophize' their symptoms more than others.[9,10]

Against this background, we sought to provide an overview of the major evidence based immune-inflammatory pathways implicated in the pathobiology of somatoform disorders. We do not aim to provide an exhaustive coverage of immune-inflammatory aberrations in somatoform disorders; instead, what we focus on is the mechanistic pathways that may link inflammation and somatoform disorders. The goal of the review was to improve our understanding of biological basis of somatoform disorders which may potentially identify novel treatment targets to ameliorate somatic symptoms and resultant distress.

METHODS

We performed an electronic search of MEDLINE through PubMed and Google scholar databases till April 2020 to identify relevant articles on inflammation and somatoform disorders. We used random combination of the following MeSH or free text terms for PubMed search;somatoform disorder*, somatization disorder, medically unexplained syndrome, hypochondriasis, somatic symptom disorder, illness anxiety disorder, Briquet syndrome, pain disorder, inflammation, neurogenic inflammation, inflammation mediators, cellular immunity, humoral immunity. Additionally, the reference list of the articles generated were hand searched to identify additional studies.

We included English language articles published in peer reviewed journals. Articles were included, regardless of their type (original article, reviews, editorials, and commentaries), as long as they discussed the biological basis of the association between inflammation and somatoform disorders. Based on these criteria, a total of 19 articles were included in the present review. Since this was a narrative overview of the topic of interest, we neither computed effect estimates nor performed a risk of bias assessment of included studies.

We examined the full text of the studies shortlisted for inclusion to identify the relevant mechanistic links or pathways discussed therein. The biological links mainly included three distinct, yet, inter-connected mechanistic pathways; cell-mediated immune activation and resultant inflammation, stimulation of TRYCAT (tryptophan catabolite) pathway, and triggering of oxidative/nitrosative stress pathways. Accordingly, the results are discussed under these headings.

RESULTS

Contribution of TRYCAT pathway

Normally, dietary tryptophan is metabolized chiefly via two pathways; by the smaller pathway into serotonin and melatonin (key for mood regulation) and by the larger TRYCAT pathway, sequentially, into multiple neuroregulatory compounds such as kynurenine, kynurenic acid, quinolinic acid, and nicotinamide. The latter pathway is preferentially activated during systemic inflammation and consequent activation of indoleamine 2,3 dioxygenase (IDO) or tryptophan 2,3 dioxygenase (TDO).[11]

This activation of the TRYCAT pathway is germane to the genesis of somatization symptoms. The Kyn/KYNA as well as the Kyn/tryptophan ratios, crucial to determining the net neuroregulatory effects, are increased in somatization compared to depression and healthy controls. Further, plasma tryptophan and kynurenic acid, which has neuroprotective as well as anti-nociceptive effects, is decreased in somatization compared to depression.[12,13] These data support notions of perturbations in the TRYCAT pathway in somatization disorder and that these perturbations are qualitatively different from what is observed in depression.[11,12]

TRYCAT activation, together with tryptophan depletion, has been linked particularly to the onset of pain and fatigue. The depletion of tryptophan has been linked to the resurgence of depressive symptoms in remitted individuals.[14] Simultaneously, it has also been associated with nociceptive effects in a wide range of medical conditions. Increased Kyn/KYNA ratio, a representing TRYCAT activation, impacts nociception in two ways. Whereas Kyn enhances pain and gut motility (which may also lead to IBS-like symptoms), KYNA has anti-nociceptive effects exerted through NMDAR antagonism and G-protein couple receptor 35 activations. These processes are further accentuated by systemic inflammation which sensitizes NMDAR as well as activates the IDO pathway which in turn increases

TRYCAT products, such as kynurenine/quinolinic acid with "depressogenic/somatogenic" potential.

Indeed, increased IDO activity and resultantly decreased serotonergic functioning has been associated with altered gut motility and increased pain sensitivity, both of which are cardinal symptoms of irritable bowel syndrome.[15] The female preponderance of somatoform disorders could be due to increased IDO responsiveness.[16,17]

Cell-Mediated Immune Activation and Inflammation

Systemic inflammation may also underlie the wide-ranging sleep disturbances noted in fibromyalgia and chronic fatigue syndrome. Sleep and systemic inflammation seem to share a reciprocal relationship with a decrease in sleep leading to elevations in pro-inflammatory cytokines, which further impairs sleep time. Cytokine alterations may also impair normal sleep physiology and architecture, altering normal NREM and REM durations. Sleep disturbances may also cause fatigue and malaise, both central to sickness syndrome. Thus, immune activation and inflammation may underpin key somatic symptoms such as pain, sleep, and fatigue [18].

Somatosensory amplification

Findings from animal studies suggest that exogenously administered cytokines can result in a heightened nociceptive experience induced by a peripheral stimulus. This suggests that peripheral pain sensations can be amplified in the brain, consequent to cytokine-dependent sensitization.[10] A plethora of studies have consistently demonstrated increased levels of systemic and central inflammation in depression, another condition with heightened pain experience. But few studies have examined this issue in somatoform conditions [19].

In this regard, using a case-control design, Euteneuer and others reported a novel finding of elevated levels of neopterin in people with somatization syndromes compared to healthy controls as well as major depression. Neopterin is a pteridine compound, known to be produced by monocytes activated by IFN-y, a known pro-inflammatory cytokine. Consequently, neopterin is an indirect marker of IFN-y activity. Persistent elevations of IFN-y stimulate dorsal horn neurons in the spinal cord, thus amplifying bodily sensations through central sensitization. Increased IFN-y can also enhance pain perception by downstream effects such as IDO and TRYCAT activation, which alters kyn/KYNA ratio and heightens pain experience as explained in the preceding section [20].

These immune-inflammatory pathways are part of a larger, integrated stress response matrix in the body that also involves the hypothalamo-pituitary-adrenal axis and autonomic nervous systems that underpin normal brain and body responses to different types of stress such as pain, arousal, emotional or psychological trauma. The stress system model of FND emphasizes the sensitization effects of early life stressors which may prime the brain-body stress system to trigger abnormally exaggerated responses to subsequent life stressors [21]. During this process, aberrant functional connectivity between the components of the stress response matrix may provide a biological substrate for amplification of normal body sensations, provoking distress, and impairment. Very few studies, though, have systematically examined this proposition [22].

The above mechanisms provide a neurobiological basis for the somatosensory amplification model of Barsky and colleagues, a popular approach employed in traditional CBT models for somatization [23]. However, it also legitimately questions the current taxonomical position of somatoform disorders, traditionally understood as physical symptoms in the "absence" of a corresponding medical basis.

Role of oxidative/nitrosative pathways

Normally, there is a balance in the body between stress-induced free radicals and anti-oxidant compounds that prevents oxidative stress and damage. Following stress, the resultant inflammatory pathway cascade produces an outpouring of reactive oxygen radicals; such as peroxides and superoxides. Owing to the direct cellular damage they induce via lipid peroxidation, such pathways may be pertinent to the genesis of physical symptoms such as muscular fatigue and pain [24,25].

Indeed, there is now credible evidence for increased oxidative stress in chronic fatigue syndrome. However, the exact mechanisms linking oxidative damage to specific physical symptoms, such as fatigue, in other words, a pathway phenotype is less clear. Researchers have

proposed an exaggerated IgM response against fatty acids and markers of oxidative stress in the muscular system such as malondialdehyde which may be central to muscle fatigue. Vindicating the role of oxidative stress further, studies have found that muscular fatigue can be delayed in exercising individuals by pre-medicating with N-acetyl cysteine, a known anti-oxidant compound [26].

Other mechanisms proposed include IgM and IgG-mediated autoimmune reactions that target neuro-transmitters such as serotonin. Increased serotonin auto-immunity is closely tied to cytokine-mediated immune activation as well as triggering of the TRYCAT pathway, leading to further depletion of serotonin. This may have implications for pain perception. In two related case-control studies, the authors found evidence for nitrosative stress in chronic fatigue syndrome and postulated that it may be a common biological pathway that explains the clinical overlap between CFS and MDD. Specifically, the authors found evidence for IgM mediated immune response against proteins which then undergo chemical modification and become immunogenic on account of nitrosative and oxidative damage. The neoepitopes generated during this process of protein modification may trigger an IgM response [27,28].

Evidence for disrupted oxidative balance with net oxidant stress has also been shown in a case-control study of subjects with DSM-5 defined somatic symptom disorder. Interestingly, the authors noted that their findings may not fully reflect brain oxidant status as only serum samples were studied and recommend cerebrospinal fluid-based studies in the future [24].

Put together, there is emerging evidence for oxidative and nitrosative stress in somatoform disorders which must be considered preliminary due to the limited literature. Unanswered questions that may be worth further investigation are whether it is possible to delineate oxidative stress biomarker signatures for different subtypes of somatoform disorders, use these markers as a predictor of treatment response and whether and to what extent there is a role for antioxidants in the treatment of somatoform disorders [28].

CONCLUSION

Signalling of peripheral and central immune-inflammatory pathways, in response to different types of stressors, may underlie a host of somatic symptoms such as pain, fatigue and insomnia commonly seen in somatoform disorders. The immune-inflammatory pathways described above are a result of cross-sectional studies in patients with somatoform disorders and hence, longitudinal studies are needed for better understanding and to delineate the complex interplay between the three mechanistic pathways which will foster novel therapeutic targets for the treatment of this difficult to treat the disorder.

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