

Stress and Inflammation: New Perspectives on Major Depressive Disorder

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Objective: The purpose of this review is to provide an integrated account of how life stress affects inflammation in the body, how the dysregulation of immune pathways is linked with depression and other chronic diseases, and which stress reduction techniques are applicable to specifically reverse these factors contributing to disease development. Stressors in the modern environment will be defined as they relate to the immune system and major depressive disorder (MDD) development. The inflammatory theory of depression will also be examined as it relates to these stressors. Lastly, research on the efficacy of various stress reduction techniques will be discussed, including specifically how they may be used to counter the inflammatory instigators of MDD. In this manner, this review will provide a cumulative roadmap for providers and patients alike to trace the development of MDD and further avenues for treatment of this complex disease.

Depression is a multifaceted disease associated with significant morbidity and mortality. In recent years, increasing attention has focused on the role of the immune system in disease development. An expanding body of evidence demonstrates that patients with MDD have, on average, increased activity of the inflammatory system. Further, evidence implicates inflammation as a fundamental neurobiological alteration in MDD. Targeting this system may thus provide beneficial effect on illness trajectory.

However, not all patients who are depressed have increased inflammation, and it remains to be determined whether the inflammation is a cause or effect of the depression phenotype. Regardless of the direction of causality, depression severity is positively correlated with a pro-inflammatory balance in the body (higher ratio of pro- versus anti-inflammatory cytokines). Given that traditional depression therapies only achieve remission

about 37% of the time,¹ reexamination of the therapeutic targets for depression is indicated. In this paper we will discuss the current theories of depression pathophysiology and the modern societal exposures which may contribute to MDD.

Method: A literature review was conducted in order to identify relevant studies on depression etiology and specific stressors of the modern world. Search strategies with specific search terms for each dimension were defined and the following databases were used for each dimension: PubMed, JSTOR, and Google Scholar. These initial database results were then expanded by analyzing the references of the most relevant articles for further results. The initial database search was conducted by selecting the top 10 search returns for each search criteria and analyzing the results of these studies. In this way the information was not selectively filtered based on findings, and the possibility of discarding potentially relevant reports was minimized. A total of 160 references were analyzed. Nine were included in the present review. References were included if they mentioned inflammatory states or markers in relation to the specified dimension of stress. There was no restriction on language.

Modern Stressors

The human body is designed to react to physical threats in the environment by upregulating the sympathetic nervous system and disrupting the immune response. This has far-reaching effects on virtually every organ system in the body. Urban society has largely overcome typical inflammatory triggers such as microbial infection and predators, but we are still wired to react to threat without much consideration as to cause. The typical “causes” of stress have thus been replaced by modern stressors that accompany urbanization, including dissolution of family structure, social

alienation, pollution, processed foods, traffic, finances, sleep disturbance and more, some of which are associated with systemic inflammation.² These stressors are represented by the pro-inflammatory response they cause, marked by cytokines interleukin 1 and 6 (IL-1 and IL-6) and tumor necrosis factor (TNF- α), transcription factors like NF- κ B, acute phase proteins like C-reactive protein (CRP), and the chronic stress marker cortisol—all of which have been observed to be elevated in depressed patients.

Social Determinants of Health

Adverse events occurring in utero³ and early childhood such as inadequate nutrition, low socioeconomic status, unsafe housing and fragmented family structure have been consistently related to an exaggerated stress response later in life, and higher lifetime rates of depression, as well as diabetes, cardiovascular disease, cancer and liver disease.⁴ These same early life stressors predict elevated levels of inflammation later in life.⁵ Psychosocial stress, or even the mere perception of it, affects brain chemistry and mood on a biological level, regulating molecular processes that set the stage for MDD and other non-communicable, chronic diseases later in life.⁶ Identifying at-risk youth early to address pathologic response patterns with appropriate early intervention may decrease propagation of the inflammatory response and worsening of depressive symptoms later in life.

Obesity and the Sedentary Lifestyle

Adipocytes are known to release pro-inflammatory cytokines (adipokines) and chemotactic factors which play a role in the overweight, low-level inflammatory state.⁷ Conversely, serum CRP levels are inversely related to intake of fruits and vegetables, which is thought to be due to the anti-inflammatory effects of the flavonoids they contain. A number of dietary intervention studies have provided evidence that dietary flavonoids are capable of modulating inflammatory cytokines and CRP production, which may explain the results of prospective cohort data suggesting that increased fruit and vegetable intake was associated with improved cogni-

tive function and reduced risk of age-related neurodegeneration.⁸ Diet is thus a target in treatment-resistant MDD, particularly when it coexists with obesity. A mental health clinician can offer simple recommendations for body fat reduction and increased consumption of fruits and vegetables.

Sleep Disturbance

Lack of sleep has detrimental effects on the body. In a study examining effects of sleep disturbance on inflammation in mouse models, Zhu and colleagues demonstrate increases in IL-6 and microglial activation in the mouse brain following 24 hours of sleep disruption. Histological results from the study further suggest that neuroinflammation induced by sleep disturbance may contribute to impairment in learning and memory and decline in cognitive function.⁹ Given that MDD is often accompanied by sleep disturbances, interventions that target improvement in sleep are important.

One practical intervention to address sleep disturbance in children and adolescents involves electronic use. Sleep disturbance is becoming especially relevant for youth using electronic screens just before bed.¹⁰ After-dark exposure to electronic screens is associated with impaired sleep, an observation which is likely compounded by the fact that electronic screens utilize a wavelength of light which the human brain associates with wakefulness.¹¹ After-dark exposure to this light throws off the circadian rhythm and can disrupt homeostatic processes necessary for health.¹² Because sleep disturbance is correlated with higher levels of circulating pro-inflammatory cytokines as well as increased occurrence and recurrence of depressive symptoms, sleep hygiene is an additional therapeutic target when pharmacologic treatment of MDD proves inadequate.¹³

Stress, Inflammation, and Depression

Implications for Mood. There is now substantial evidence that psychological stress, a well-known precipitant of mood disorders, can increase inflammatory activity,¹⁴ and the presence of this inflammation may confer risk for MDD development. Depressed patients with increased inflammatory biomarkers are more likely

to be resistant to conventional antidepressant therapy, while inhibition of these markers improves mood as well as treatment response, pointing to the role of inflammation in disease severity.¹⁵

The implication of specific immune genes and inflammatory markers in MDD calls for a reexamination of the current treatment model for depression. Instead of directing clinical and research attention on the monoamine system, investigation of possible immune targets is justified. In a narrative review of inflammation and depression by Young *et al.*, the authors conclude that studies to date have demonstrated mixed results but that further research is warranted.¹⁶ Research involving the application and monitoring of immune-targeted therapies for appropriate patient populations would be critical in reimaging our approach to MDD management moving forward.¹⁵

Final Remarks

Clinicians Need to Counsel Patients About Stress.

Reducing stress reduces inflammation, and if MDD is at least in part an inflammatory disease, providers should give weight to this component of disease pathophysiology when counseling patients.

As the number of chronic conditions in society increase, so does the necessity for preventative stress counseling. Stress counseling is rarely offered by physicians—only 3% of primary care visits included this measure on a national study from 2006–2009. And when it is offered, it is often as a response to chronic disease flare-ups.¹⁷ As more diseases of modernity are shown to have an inflammatory basis, and in light of the fact that stress is shown to promote inflammation, stress reduction seems an almost necessary preventive measure that should be taken by anyone living in modern urban environments. Evidence-based stress reduction techniques are readily available to correct the immune dysregulation which often accompanies MDD, including mindfulness-based stress reduction (MBSR), yoga, nature exposure, and physical exercise. These simple, low cost interventions could help prevent development of chronic diseases like

MDD and have beneficial effects on those patients who have already suffered the consequences.

Take Home Summary

Links between stress, inflammation, and depression are emerging such that it may be possible to trace the effects of life stressors on mood. Behavioral modifications of these stressors may offer avenues for or adjuncts to disease treatment and understanding.

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