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From cells to society: untangling the web of stress, inflammation, and social determinants of health

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A Viewpoint on the Frontiers in Science Lead Article

A multiscale inflammatory map: linking individual stress to societal dysfunction

Key points

- Chronic inflammation links chronic psychosocial stress and various disorders through a complex bidirectional exchange between neuroendocrine and immune systems.
- Inflammatory stress-related non-communicable conditions are a major challenge for 21st century medicine, and their impact is amplified by various health disparities, including socioeconomic inequalities, together with racial, ethnic, sex, gender, and lifestyle factors.
- Mathematical models have the potential to improve our understanding of the interface between stress, inflammation, and disease, as the response to stress is an emergent property resulting from a non-trivial convolution of the networked components of a complex system.

Introduction

The *Frontiers in Science* Lead Article by Vodovotz et al. (1) examines several important ideas. First, it focuses on "stress" as the point of convergence of a diverse array of factors encompassing everyday life. It explores stress beyond the physiological realm and expands the relations between stress and behavior, lifestyle, race, sex, gender, and socioeconomic factors. The overarching hypothesis is that "everyday life" stimuli drive inflammation and complex biological responses. Using the activation of the inflammatory response as the underlying physiological driver, Vodovotz et al. connect cellular responses in peripheral tissues and (central) neural processes, establishing the bidirectional influences of the

inflammatory response on the brain and *vice versa*. Their work explores the intriguing idea that "[…] *inflammation acts as an embedded, multiscale driver connecting most or all stressors affecting individuals to large-scale societal dysfunction* […] *which in turn drive inflammatory stress via a positive feedback loop*." The central hypothesis advocated by the authors argues that persistent deregulation of "*these interdependent inflammatory and neural processes* […] *can culminate in a multiscale, runway, feedforward process that could detrimentally affect human decision-making and behavior at scale*." At the same time, the authors advocate using mechanism-based, mathematical models for describing the host's response to everyday stress in a quantitative and predictive manner to express the chronic derangement of physiological states. When formalized using quantitative mathematical models, the expression of these concepts enables us to appreciate complex dependencies and emerging behaviors, thus laying the conceptual foundations for developing computational tools that could provide insightful public health policy directions and guidelines when integrated with large-scale, population-level data. This article is one of the most recent in a long series of publications by Vodovotz and coworkers, aiming to demonstrate the power of mathematical modeling to improve our understanding of the host response to stress, inflammation, and trauma[1].

The evolving concept of stress

The groundbreaking work of Hans Selye has been pivotal in shaping our understanding of stress. Selye recognized that damage from "non-specific nocuous agents" appears in the form of a syndrome, the symptoms of which are independent of the nature of the damaging agent (2). Selye formalized and applied the general adaptation syndrome (GAS) theory to the integrated and interrelated adaptive reactions to non-specific stressors (3). GAS comprises three stages: alarm, resistance, and exhaustion.

The concepts of stress and GAS have since evolved. We now realize the large variety of forms stress can take (4), including physiological (cold, heat, radiation, noise, chemical, metabolic, cardiac, etc.) and psychological (emotional, cognitive, perceptual, psychosocial, etc.). The stress system is intertwined with, affects, and is affected by various physiological systems, particularly those in the brain responsible for cognitive and/or executive functions (5). Humans respond to stress by activating a complex network of interactions involving the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS). The brain plays a central role by enabling the perception of stress, activating the HPA (thus regulating the release of stress hormones), activating the SNS, and engaging cognitive and emotional responses (6). The stress response is adaptive and activated to deal with the stressor (7); however, prolonged activation of certain brain areas (the hippocampus, prefrontal cortex, and amygdala) can impact cognitive functions, thus hampering the stress response (8). Unlike the original view that stress is always "bad," stress can play a multifaceted role, being both beneficial and detrimental, depending on intensity, duration, and individualized perception and response to it.

Chronic stress, allostasis, and allostatic load

Stress is a physiological or psychological disturbance in the dynamic balance of a complex system. Stress is permanently present in everyday life, whether predicted (such as daily or seasonal cycles) or unpredicted—including acute (i.e., short-term) or chronic (i.e., long-term) events driven by outside factors. The realization that chronic exposure to psychological or psychosocial stress links to a wide range of adverse health outcomes guides our desire and need to understand the implications of chronic stress. The early work of Selye, as well as an increasing body of recent research (9), has identified the inflammatory response to long-term stress as a significant contributing factor to these adverse health outcomes (10). However, it is still unclear how to determine the point at which chronic stress transitions to an irreversible physiological change, in turn leading to disease. Even more fascinating are the enduring effects of stress, manifested long after the stressful period, especially in the context of childhood adversity (11), and the inter-generational transmission of irreversible stress effects (12). One approach to this question is to understand and describe the entire cascade connecting the host's environment, the systems enabling perception of the environment (brain), and the pathways for communicating information from the brain (central nervous system), eventually reaching peripheral physiological systems. This is undoubtedly a monumental task, primarily because of uncertainty in describing the intrinsic (patho) physiological mechanisms, the extrinsic environmental factors, and genotypic diversity.

The realization that stress, whether physiological or psychological, is present in everyday life led researchers to revisit homeostasis in the context of allostasis, eventually redefining the overall perception of stress and its role in human health. Allostasis (stability through change) is necessary to adjust homeostatic mechanisms and cope with daily stress (13). The idea that dealing with stress requires adjustments of homeostatic set points expands the *constancy of the milieu intérieur* concept that had been a pillar of physiological homeostasis (14). This adaptation is vital to survival, yet persistent stress activation can have detrimental effects in the long run (15). The chronic activation of stress mediators results in the dysregulation of adaptive mechanisms, leading in turn to physiological "wear and tear," i.e., accumulation of allostatic load, which reduces the ability of the host to flexibly cope with subsequent stressful perturbations. The reactive scope model (RSM) offered a conceptual framework for quantifying allostasis, acknowledging the variability and complexity in individual reactions to stress (16). Mathematical models have been developed to quantify these stress responses and identify stability ranges in homeostasis (17). Goldstein suggested a novel approach to model interactions between physiological systems using principles from control engineering, specifically in terms of homeostasis,

1 These publications can be identified here: https://pubmed.ncbi.nlm.nih.gov/?term=Vodovotz+Y&sort=date.

multiple effector interactions, and resetting set points (18). This model conceptually demonstrated that the activation of effectors in response to changes in a monitored variable leads to wear and tear, reducing effector efficiency, which is analogous to the physiological wear and tear triggered by stress response activation.

Allostasis and allostatic load have further facilitated a more nuanced understanding of the processes involved in shaping individual variations in resilience and vulnerability to different physiological stressors. Resilience maintains physiological, developmental, and behavioral stability in stress response (19). It involves the activation of allostatic mechanisms and is influenced by factors such as sex, gender, ethnicity, and genetics (20). Stress resilience emerges from complex interactions between central (brain) and peripheral (body) signaling pathways. The HPA axis and SNS are key to this process, which is crucial for brain-body communication and individualized adaptation to stress (21). Mathematical models (22) have investigated the effects of chronic stress habituation and individual variability in circadian dynamics in response to chronic stress, focusing on biochemical models of the HPA axis (23). It was determined that allostatic habituation to chronic stress requires changes in the feedforward and feedback mechanisms of the HPA network (24). Additionally, individuals with higher pre-stress adrenal sensitivity are more likely to experience chronic stress sensitization after habituation. Furthermore, a personalized analysis of the HPA axis' regulatory dynamics revealed a trade-off between its primary functions: maintaining homeostasis and responding flexibly to stress.

Inflammation: the link connecting stress to disease

Put simply, stress is the body's reaction to threats,[2] while inflammation is a biological response to injury and infection involving immune cells, blood vessels, and molecular mediators. However, stress is more than just a feeling. It is a physiological response to any actual or perceived threat. The stress response will activate the HPA and SNS and release stress hormones, whereas inflammation will activate the immune cells to release cytokines and chemokines to promote healing. However, the interaction between cytokines and the HPA axis is a prime example of the complex crosstalk between the immune and neuroendocrine systems. This bidirectional communication is crucial in the body's response to stress and inflammation. Therefore, it is no surprise that diseases commonly associated with chronic inflammation are also associated with stress, whereas perceived stress is associated with elevated concentrations of inflammatory biomarkers (25).

Understanding this bidirectional link is crucial for appreciating the role of stress in human health. Although stress activates the stress response, it is not evident why dysregulation in the stress response component would translate to disease development. However, the whole picture changes once we realize that stress impacts the entire cascade, eventually activating an inflammatory response (9). Evidence illustrated that both acute and chronic stress are associated with increased inflammatory activity as quantified by increased levels of inflammatory cytokines. Understanding this connection is paramount for understanding the transition—the tipping point (26)—between acute and chronic conditions leading to disease.

Societal health disparities, stress, and inflammation

Through the allostatic lens, stress permeates our everyday life experiences. However, we are still unaware of what transpires within the brain and across our body when experiencing stress, such as anxiety arising when exposed to news of violence, turmoil, and conflict, or when dealing with the fast-paced and high demands of our daily lives. In turn, our response to stress can disrupt our body's natural rhythms, leading to unhealthy habits such as overeating, insufficient exercise, and poor sleep patterns, all contributing to an unhealthy lifestyle. Factors like poverty, sex, gender, racial and ethnic discrimination, and limited access to education and economic opportunities exert additional stress, leaving a lasting mark on the brain and body. Such experiences can have long-term health repercussions, increasing the risk of chronic, non-communicable diseases such as heart disease, type 2 diabetes, depression, substance abuse, antisocial personality disorder, and dementia. It is accepted that the major health challenge of the 21st century will revolve around stress-related non-communicable diseases (27). Health disparities, defined as variations in healthcare access and health outcomes, are closely linked with stress and overall health (28). Factors such as race, sex, gender, socioeconomic status, access to healthcare, education, and quality of living conditions create these disparities. These factors lead to inequalities that frequently cause chronic stress, thereby increasing the risk of various health issues. Thus, disparities perpetuate a vicious cycle where people already at a disadvantage experience more significant health challenges that further amplify their disadvantages.

Social support, stress, and inflammation

Recent scientific research has provided empirical evidence establishing a quantitative relationship between social relationships and health outcomes, particularly in the context of inflammatory biomarkers. Historically, the connection between social factors and health was inferred through qualitative and abstract criteria. However, contemporary studies have concretely linked social support networks—including spouses, family members, and friends—with specific inflammatory markers in the body (29). These studies suggest that social strain or relationship stressors can negatively impact biomarkers more significantly than the positive effects of supportive social interactions, implying that negative social experiences may influence inflammatory processes more than the positive effects of social support. The shift from qualitative assessments to more

2 Stress can be defined as a state of worry or mental tension caused by a difficult situation, according to the World Health Organization.

quantifiable measures advances our understanding of the complex interplay between social dynamics and physiological health, shedding light on the fundamental cellular and molecular links between psychosocial stress and inflammation (30).

Racial/ethnic disparities, stress, and inflammation

Scientific research indicates a heightened prevalence of low-grade inflammation in Hispanic and African American pediatric populations when compared with their white counterparts. This disparity in inflammatory risk is more pronounced in children of Hispanic and African American descent who have parents born outside the United States, as opposed to those whose parents were born in the United States. These findings suggest a complex interplay of racial, ethnic, and sociodemographic factors contributing to varying levels of inflammation among different child populations, with particular emphasis on the influence of parental nativity on these health outcomes (31).

Sex, gender, stress, and inflammation

Women exhibit a significantly higher risk of developing stress-related disorders. Concurrently, the role of inflammation in the etiology of depression has been increasingly recognized. Specifically, augmented activity in the locus coeruleus-norepinephrine (LC-NE) system in women may lead to an overproduction of norepinephrine (NE), which in turn could elevate systemic inflammation levels (32). Thus, the exaggerated stress-induced inflammatory response observed in women might contribute to a self-perpetuating cycle that involves an enhanced release of interleukin-1 beta (IL-1β) in the periphery. Interestingly, men exhibit higher levels of inflammation in the base case, which may partly explain the higher levels of oxidative damage, although a weaker pro-inflammatory response is activated against acute challenges (33).

Socioeconomic status, stress, and inflammation

Socioeconomic status (SES), typically characterized by factors such as income level, educational attainment, and occupational category, is empirically linked to an increased risk for various diseases and psychopathological conditions. However, recent analyses established the likely missing link, indicating that low SES is associated with marked increases in inflammation as measured by inflammatory biomarkers (34). A comprehensive analysis of available data suggests that individuals with lower SES exhibit significantly higher levels of system inflammation (35).

Lifestyle, stress, and inflammation

The increased incidences of chronic systemic illness suggest that unresolved chronic inflammatory activation renders the host unable to respond to danger signals. Lifestyle changes, new to our evolutionary process, have been considered as possible inflammatory instigators. Although particular emphasis has been placed on nutrition, several associations exist between health-promoting lifestyle behaviors, stress, and markers of inflammation (36). A most prominent lifestyle disruption likely relates to biological (circadian) rhythms (37).

Income, education, stress, and inflammation

To advance our understanding of the role-specific components of SES that impact inflammation, studies have attempted to associate inflammatory markers with education and income. Both were negatively correlated with inflammatory markers, but the relation was eliminated after adjusting for income (38). The likely explanation is that health-damaging behaviors, leading to increased inflammation, were negatively correlated with income.

In recent years, we have witnessed the significant impact the factors above had on the substantial ethnic, gender, and socioeconomic disparities in COVID-19 mortality (39).

Decoding stress: the role of mathematical modeling in understanding the interface between stress, inflammation, and health dynamics

Despite substantial progress in elucidating the effects of stress on various stress-responsive physiological systems—encompassing the HPA axis, SNS, metabolic and immune systems, cerebral function, and peripheral organ functionality—considerable gaps in knowledge persist. A formidable challenge resides in synthesizing stressor impacts across diverse physiological strata, extending from molecular and cellular dimensions to neural circuitries, systemic interplays, and their repercussions on population health. The key reason why mathematical models have the potential to enable our understanding of the role of stress is that the response to stress is an emergent property, the result of a non-trivial convolution of the networked components of a complex system. Although several components of stress and stress mediators have been identified, how they come together is a puzzle waiting to be solved. Mathematical formalism offers a powerful tool for rationally integrating these components and systematically analyzing the network's potential perturbations and signal propagation. These models hold the potential for delineating the aggregate consequences stemming from the intricate web of interactions among various allostatic mediators and discerning the nuances of individual variations in physiological signal regulation. Romero et al. (40) beautifully articulated the challenges in stress modeling and the opportunities offered by developing mathematical models, while emerging technologies, such as wearable sensors for stress detection and machine

learning algorithms, provide exciting avenues for further enriching our understanding of this intricate puzzle (41). As our understanding of allostatic mechanisms deepens, mathematical modeling will become increasingly vital, enabling more precise characterizations of stress responses and a stronger conceptual framework for understanding physiological regulation.

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IA: Conceptualization, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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