



Stress, Coping, and Immunologic Relevance: An Empirical Literature Review

Chandra Sekhar Tripathy¹, Sarvodaya Tripathy², Bandna Gupta³, Sujita Kumar Kar³

Departments of ¹Psychiatry and ²Microbiology, M.K.C.G. Medical College, Brahmapur, Odisha, ³Department of Psychiatry, King George's Medical University, Lucknow, Uttar Pradesh, India

Stress is an inevitable phenomenon in life. Stress plays a pivotal role in regulating the body's physiology. Stress also improves the survival skills of an individual. However, when stress becomes unmanageable, it starts affecting the individual adversely. The adverse effects of the stress alter the normal physiology and the mental well-being of the individual. People attempt to cope with their stressor using various coping strategies. Adapting coping strategies may help in successful handling of stress. Maladaptive coping strategies, on the other hand, though control stress, are often transient and may result in the impairment of mental health. Evidences suggest that stress significantly affects the immune system of the body. The effect of stress on the immune system may depend on the nature and severity of the stressor. Ineffective regulation of stress results in immune dysregulation. Effective coping strategies for handling stress might be useful to correct the immune dysregulation.

Key words: Stress, coping, immune regulation

INTRODUCTION

The term "Stress" has been used very commonly in literature, particularly in the context of mental illnesses. Stress has been defined in various ways. In simple terms, stress may be defined as "the response within an object (individual), which is inherent to the object and experienced in response to an external force."¹ Lazarus defined stress as "a relationship between the person and the environment that is appraised as personally significant and as taxing or exceeding resources for coping."^{1,2} Both Cox and McGrath have defined stress as "the imbalance between the perceived demands placed on an individual and his or her perceived capability to deal with the demands."³

Stress response can be physiological as well as psychological. The physiological response can be elicited by the alteration of cardiorespiratory function, skin temperature, muscle tension, and change in stress hormone (e.g. glucocorticoids) levels. The psychological manifestations, on the other hand, occur in the form of anxiety and subjective distress.⁴

Coping refers to the strategy that an individual adopts to deal with the stressor. Tudorache *et al.* have defined stress coping styles as "a coherent set of individual behavioural and

physiological differences in the response to a stressor which remain consistent across time and context."⁵ Stress coping style is highly influenced by psycho-socio-cultural factors. Recent research in experimental animals (zebrafish larva) revealed that biological factors such as difference in the cortisol response also determine the stress coping style.⁵ This article aims at exploring the immunological basis of stress and coping as well as their relevance in stress management. Literature search was done using the keywords "Stress," "Coping," and "immunological changes" in the Google Scholar and PubMed databases.

DETERMINANTS OF OUTCOME OF STRESS

The experience of stress varies between individuals and is determined by several variables such as support system of the individual, severity of the stress, selection of coping strategies, and past experiences of the individual. The outcome of stress is not always determined by the individual's ability to handle stress. That is, a positive outcome is not necessarily associated

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Corresponding Author: Dr. Sujita Kumar Kar, Department of Psychiatry, King George's Medical University, Lucknow, Uttar Pradesh, India. Tel: +91-9956273747; Fax: +91-0522-2258805. E-mail: drsujita@gmail.com

with adequately managed stress.⁶ Cognitive appraisal about stress too determines the responses to stress. Kessler *et al.* mentioned that all people exposed to stressful life events or chronic stressors do not develop significant psychological impairment, only the vulnerable individuals do.⁷ Adequacy of social support and selection of coping strategies are important determinants of stress response.⁷

Various factors play a pivotal role in defining vulnerability to stress. These factors can be biological, psychological, and sociocultural. The biological factors include inherited traits (genetics), neuro-hormonal disorders, and preexisting medical disorders. The psychological factors can be early life experiences, personality factors, existing psychiatric disorders, substance use disorders, and lifestyle-related factors. Sociocultural factors which are decisive for vulnerability are parenting, cultural values, social support, workplace stress, stigma and isolation. An individual's vulnerability or resilience to stress is also decided by various other factors (age, gender, and intelligence). Certain personality characteristics such as optimism, self-efficacy, self-esteem, locus of control, hostility, social inhibition, and negative affectivity also determine the vulnerability.⁸

A recent study on experimental animals (rats) revealed that better emotional controllability results in healthier stress resilience.⁹ In another animal study, it was found that there is continuous interaction between the coping strategy and behavioral training. The interplay of positive coping strategy and adaptive behavioral training determines the resiliency to stress, which is evident in the form of specific changes in brain and stress hormone.¹⁰

Lazarus has described various self-regulatory mechanisms that determine the outcome of stress.¹¹ The self-regulatory processes can act either directly or through palliative activities. The directly acting self-regulatory process basically targets the complex interplay of individual with its environment. The self-regulatory palliative activity may be an intrapsychic process or somatic-targeted mechanism. The intrapsychic processes operate by using various cognitive appraisals such as denial, emotional distancing, and attention deployment. Pharmacological treatments, relaxation exercises, and even the biofeedback technique regulate stress by specific somatic mechanisms.¹¹

Health-related behaviors are an integral part of lifestyle. The health-related behaviors vary across different populations. These health-related behaviors can include eating, exercise, substance abuse, and sleep hygiene. Evidences suggest that many health-related behaviors are associated with stress.¹² These health-related behaviors may be used as a coping strategy to combat stress. To cope with stress, individuals may adopt certain health-related behaviors either in increased

or decreased frequency. For example, under stress, people may abuse substances, drive recklessly, avoid exercise, eat excessively, or avoid eating.¹² High stress may be associated with the consumption of more fast foods and high-calorie diet.¹² Change or adoption of a particular health-related behavior as coping response to stress depends on many variables such as sociodemographic characteristics, culture, and personality of that individual.¹²

VARIATIONS IN STRESS AND COPING

The age-wise distribution of population varies across the globe. Majority of the developed countries have population distribution in the form of an inverted pyramid indicating increased elderly population than younger ones, whereas in the developing and underdeveloped countries, the population distribution is in the form of an erect pyramid (young population being the major bulk). The nature and experience of stress and coping varies according to age. The variations in stress and coping in different ages can be explained by the variations in the environment and life stage-related changes.¹³

When compared among genders, females perceive life event as more stressful and score high on chronic stress as well as day-to-day life stresses.¹⁴ Coping styles of women also differ from that of men. Women often prefer to use emotional and avoidance coping, whereas men often cope by inhibition of emotions.¹⁴ Coping by psycho-somatic distress is again reported to be common in women than men.¹⁴

Stress is an evolving phenomenon, so also is coping. Living circumstances and the process of aging have a substantial influence on stress and coping.¹⁵ Personal values and beliefs also determine appraisal about stress.

Evidences suggest that individuals with better sense of humor often use problem-solving coping strategies and have a positive reappraisal of problem than individuals with lower level of humor.¹⁶ Individuals with higher level of humor often experience little anxiety and stress with response to the day-to-day problems in comparison to individuals with lower level of humor.¹⁶

Pargament has proposed the concept of religious coping.¹⁷ According to Pargament, religion plays a pivotal role in coping with stress.¹⁷ Religion is an integral part of our social system. Religious concepts are readily available. Evidences suggest that individuals who are more religious use religious coping more frequently.^{17,18} He has described that religious coping subserves many functions such as finding the meaning of life, effort to reach close to God and others, and mastering control as well as transformation of life.¹⁹ Religious coping can be used positively or negatively. The positive ways of religious coping are perceiving stressor as an opportunity, acknowledging

God's blessings, and accepting God as a partner.²⁰ Similarly, the negative ways of religious coping are perceiving stressor as punishment, nonreliance on God, and passively dependent on God to solve problems.²⁰

Recently, the use of electronic gadgets has increased substantially worldwide. Excessive indulgence in gaming, chatting, shopping, and watching sexual or aggressive content may occur in response to stress. A major purpose of use of the Internet is entertainment. Internet (technology) addiction has emerged as a challenging issue. Children and adolescents are more vulnerable to get affected by this.²¹ In a large-scale survey on Internet use among community population, it was found that people who are addicted to the Internet often use it as a coping behavior to combat loneliness and depression.^{22,23} Similarly, evidences also suggest that adolescents cope with their loneliness by indulgence in online as well as offline activities (gaming, watching videos, etc.).²⁴ Individuals with poor social skills and poor coping ability are also likely to get involved in compulsive use of gadgets.^{22,25}

IMPACT OF STRESS

Impact of stress on health is enormous. Stress can be a predisposing, a precipitating, as well as a perpetuating factor for various physical and psychiatric disorders. Individuals exposed to stress are commonly predisposed to cardiac illnesses (hypertension and coronary artery disease), stroke, diabetes mellitus, gastrointestinal disorders (peptic ulcer and irritable bowel syndrome), recurrent infections, obesity, sleep disorders, depressive disorder, anxiety disorder, and substance use disorder. Stress can precipitate or exacerbate asthma, psoriasis, autoimmune conditions, depression, adjustment disorder, dissociative disorder, somatoform disorder, other stress-related disorders (posttraumatic stress disorder and acute stress reaction), psychosis, bipolar affective disorder, substance use disorder, and sleep disorder.

The presence of physical and psychiatric disorders in turn increases stress [Figure 1]. The vicious cycle of stress and illness continues, one aggravating the other. This vicious cycle is the potential target of intervention. Prompt treatment of the disorder (illness) helps in adequate handling of stress which in turn beneficial in the effective management of the disorder (illness).

IMPACT OF COPING

Selection of coping strategy is an important determinant of the outcome of stress. Individuals who experience stress choose various coping strategies. Selection of a coping strategy depends on the familiarity of the individual with that

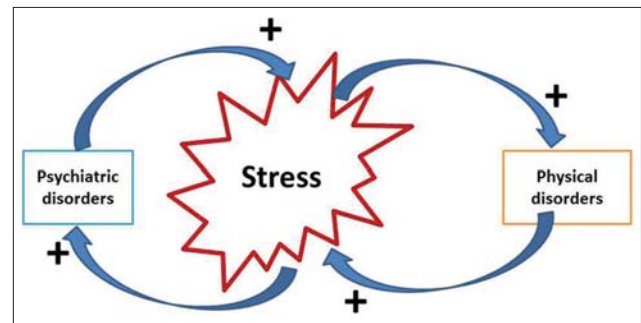


Figure 1: Modulating the role of stress in physical disorders and psychiatric disorders

coping strategy, ready availability of the strategy, personality of the individual, nature and severity of the stressor, and sociocultural characteristics of the individual.

Selection of maladaptive (negative) coping strategy leads to the development of disturbances of emotion and conduct. It may lead to poor quality of life. Maladaptive coping strategy may result in lifestyle-related disorders, psychiatric disorders, poor interpersonal functioning, and impairment in the functioning of the individual.²⁶

IMMUNOLOGIC RELEVANCE OF STRESS AND COPING

Stress produces immune activation, which is mediated by autonomic nervous system. The immune system, which includes spleen, bone marrow, thymus, lymph nodes, and other lymphoid tissues of the body, is innervated by sympathetic fibers. The immunological cells have differential distribution of adrenergic receptors on them. This differential distribution determines responsiveness to adrenalin and thus to stress.²⁷ The immunological cells in the body also respond to epinephrine, norepinephrine, cortisol, melatonin, β -endorphin, enkephalin, prolactin, and growth hormone.²⁷

Stress-related immunological modulation grossly influences the social, sexual, and eating behaviors as well as the mood. It also affects substance use behavior, sleep behavior, and thermoregulation through immunological modulation.²⁷

Chronic stress produces several mental illnesses and physical disorders, which are mediated through alteration in the physiological and biochemical parameters as well as psychological well-being.²⁸ Stress produces several immunological changes in the body, which can be attributed to the abovementioned alterations. Stress results in the activation of the genes that code for various markers of inflammation.²⁸ Chronic stress produces microglial activation in various stress-sensitive regions of the brain in experimental animals (rats).²⁹ There are stress-linked signaling

molecules (corticosterone and norepinephrine) which regulate the activation of microglial cells depending on the exposure intensity and duration of stress.³⁰ The microglial cells in the brain have a significant role in immune regulation. Microglial activity determines the process of neurodevelopment, and its dysfunction has been implicated in the pathogenesis of several neuropsychiatric disorders including neurodevelopmental disorders.³¹ Hence, the stress-mediated alteration of microglial activity brings immunological changes, which are associated with health hazards.

Evidences describe about specific biological changes in the body in response to stress. The integrity of hypothalamo–pituitary–adrenal (HPA) axis and its link with limbic system determines both stress resilience and vulnerability.³² The HPA axis also plays a vital role in maintaining the homeostasis in the body. When the severity of stress is high and the duration of exposure is long, it is likely to breach the homeostasis, which may alter the immune response.³³ Sapolsky *et al.* have mentioned that glucocorticoids, which are induced in stress, act in a beneficial way at normal-to-moderate levels, and they are suppressive for the immune system at high levels.³⁴ Glucocorticoids have multifaceted actions in response to stress. Glucocorticoids play a major role in sensitizing the body's immune system to combat stress. It suppresses the overactivity of immune system in response to stress and moderates the immune response of the individual for subsequent stressful situations.³⁵

Adverse childhood experiences are considered as significant stressors which affect the HPA axis and other stress-responsive neurobiologic systems.³⁶ Early-life adversities are perceived as stressful experiences. Evidences suggest that individuals subjected to early-life adversities have epigenetic changes such as DNA methylation.³⁷ DNA methylation may involve the glucocorticoid receptor gene, which is very sensitive to stress due to early-life adversities.³⁵ Glucocorticoids are important immune modulators. Hence, DNA methylation of the glucocorticoid gene is likely to adversely affect the process of immune regulation. The psychological after-effects of adverse childhood experience may be mediated through immune dysregulation driven by the above epigenetic mechanism.

Stress produces oxidative damage in the brain and various other organs of the body. Inflammatory reaction is a common immunological response in the body. Activation of various inflammatory markers in response to stress results in alterations in oxidative as well as nitrosative pathways in the brain.³⁸ Evidences suggest that stress causes increase in the level of markers of inflammation such as acute-phase reactants, interleukin 1, interleukin 6, and interferon gamma.³⁹ These mediators are also increased in depression,³⁹ which

indicates the involvement of a common immunological pathway in stress response and depression. This association also explains the causative role of stress in depression through immune dysregulation.

Segerstrom and Miller in their meta-analysis concluded that acute stressors that last for minutes can lead to an upregulation of innate immunity and downregulation of some functions of specific immunity. Brief stressors such as examinations tend to suppress cellular immunity without harming the humoral immunity.²⁷

Acute stress administered immediately before the introduction of an antigenic challenge significantly enhances a cutaneous delayed-type hypersensitivity response. In contrast, chronic stress suppresses cutaneous immune response as evidenced in animal (rodents) studies.⁴⁰ Chronic stressors, on the other hand, are associated with the suppression of both cellular and humoral immunities. Some evidences also support the dual role of chronic stress in the form of enhanced immune response as well as simultaneous immune suppression.²⁷

A biphasic immunologic response to stressor has been elicited from animal studies. Migration of T-lymphocytes occurs toward the skin surface in acute stress and away from the skin surface in chronic stress.²⁷ The above mechanism might be responsible for flare of immune-mediated dermatological conditions such as psoriasis after acute stress.

The body's immune system is generally very flexible. In healthy adults, significant alteration in the immune system may happen in response to stressor without causing any clinical manifestations. However, with increasing age, the flexibility reduces. This leads to compromised functioning of the self-regulatory mechanisms. The immune system also responds poorly to any stimulus with increasing age.

Stress facilitates the release of chemokines and oxidative stress markers. Chronic stress is often less controllable, and its impact is often significantly negative.

Pharmacological agents may be used to target the immune mediators of stress for the treatment and prevention of stress-related disorders. Recent evidences suggest the role of cholecystokinin-2 receptor antagonist in reducing stress-induced neuronal inflammation.²⁸ Inflammatory markers regulate the activation of N-methyl-D-aspartate (NMDA) glutamate receptor; hence, NMDA blocker might have a potential role in blocking the inflammation. Similarly, anti-inflammatory agents (COX-2 inhibitors) might also mediate the stress-induced neuronal inflammation.³⁸ Tumor necrosis factor- α (TNF- α) and nuclear factor-kappa B (NF- κ B) are involved in stress-induced neuro-inflammation; hence, the pharmacological agents that inhibit the action of TNF- α and NF- κ B might be useful in preventing the negative health outcome of stress.³⁸

If an adaptive coping can effectively combat stress, it is likely to maintain the immunological stability of the individual. If an individual chooses an adaptive coping strategy in response to acute stressor and it becomes a habitual phenomenon to deal with stress, then immunologic imbalance might not happen. Evidences suggest that use of an adaptive coping strategy like forgiveness helps in reducing the stress response and the physiological reactions mediated by stress.⁴¹ It is likely to improve the immune system functioning. Optimism associated with or resulted from healthy coping improves the immune system by increasing the population of helper T-cells and natural killer cells.⁴² A study conducted on experimental animals (mice) revealed that different coping strategies bring out different immunological changes, which remain stable over time. In that study, the mice involved in passive coping strategies had lower hypothalamic and splenic mRNA expression for interleukins than the group with active coping strategy.⁴³ It can be assumed that an effective coping strategy can prevent the untoward outcomes associated with stress and effectively modulate the immune system. There is a paucity of literature studying the impact of individual coping strategies and their corresponding immunologic changes. Future studies focusing on the immunological changes associated with various coping strategies may give an insight into this and help clinicians to recommend specific coping strategies for specific desirable immunomodulation. It is worthy teaching individuals about healthy coping strategies (problem-solving and emotion-focused strategies) and their implications. At the same time, the maladaptive coping strategies (e.g. substance use, blaming, negative appraisal of event, and avoidance) need to be discouraged. As coping is a survival skill, use of adaptive coping strategies might attribute to the development of positive health.

IMMUNOLOGICAL BIOMARKERS OF STRESS AND COPING

Immunological biomarkers may be useful to estimate stress and can be a potential measure of effective coping. As stress alters the activity of the central nervous system, autonomic nervous system, as well as endocrine system, the biomarkers are related to these systems. A recent study evaluated the influence of psychosocial stress on serum and salivary biomarkers by administering Trier Social Stress Test.⁴⁴ In response to stress, there was an increase in the levels of various salivary steroids, salivary amylases, adrenocorticotrophic hormones, and salivary α -amylases. Salivary cortisone was found to be the most sensitive stress biomarker, which also has a significant correlation with the measures of autonomic stress response.⁴⁴ Stress produces the

activation of granulocytes, whereas relaxation reverses this process. Granulocyte surface lactoferrin can be a sensitive indicator of stress.⁴⁵ Glucocorticoids and certain cytokines act as potential biomarkers of stress, which reflects the breach in the physiological homeostasis after a stressful event.⁴⁶ A single biomarker is not enough in explaining the complex process of stress. Multiple biomarkers should be estimated for stress.⁴⁷ The therapeutic interventions including both pharmacological and psychological reduce stress and related disorders by restoring the biological imbalance caused due to stress.

CONCLUSION

Stress and coping are two important individual, specific elements that constantly interact and determine illness or wellness. Understanding stress and coping in an individual will help for stress management and improvement in coping skills. As stress is an integral part of life, improving coping skills will be useful in changing the vision toward life. Successful management of stress and adoption of adaptive coping strategy will improve the personal and interpersonal functioning and quality of life and will maintain the immunological balance.

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