



## What Stress Means for the Invulnerable Reaction

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**Received:** 27-April-2023, Manuscript No. IJMRHS-23-97194; **Editor assigned:** 01-May-2023, Pre-QC No. IJMRHS-23-97194 (PQ); **Reviewed:** 13-May-2023, QC No. IJMRHS-23-97194 (Q); **Revised:** 23-May-2023, Manuscript No. IJMRHS-23-97194 (R); **Published:** 30-May-2023, J-invoice: J-97194

### ABSTRACT

*When faced with a stressor, the body initiates physiological changes to help cope with the situation. However, if stress responses are constantly activated, such as through the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes, it can lead to the continual production of glucocorticoid hormones and catecholamines. The expression of glucocorticoid receptors on immune cells can interfere with the function of NF- $\kappa$ B, which regulates cytokine-producing immune cells, while adrenergic receptors can activate the cAMP response element binding protein and trigger the transcription of genes encoding various cytokines. These changes in gene expression can disrupt immune function, leading to immune dysregulation. There is compelling evidence from animal and human studies that the extent of stress-related immune dysregulation is significant enough to affect overall health.*

**Keywords:** Stress, Immune cells, Physiological changes

### INTRODUCTION

Scientists and clinicians have been interested in the field of Psychoneuroimmunology (PNI), which studies the interactions between the Central Nervous System (CNS), the endocrine system, and the immune system, and their impact on health. The modulation of the immune response by the CNS is mediated by a complex network of signals that function in bi-directional communication among the nervous, endocrine, and immune systems. The Hypothalamic–Pituitary–Adrenal (HPA) and the Sympathetic–Adrenal Medullary (SAM) axes are the two major pathways through which immune function can be altered.

Lymphocytes, monocytes or macrophages, and granulocytes have receptors for many neuroendocrine products of the HPA and SAM axes, such as cortisol and catecholamines, which can cause changes in cellular trafficking, proliferation, cytokine secretion, antibody production, and cytolytic activity. For instance, the treatment of Peripheral Blood Leukocytes (PBLs) with catecholamines in vitro results in the suppression of interleukin-12 (IL-12) synthesis and an increase in IL-10 production. This can cause a shift in the phenotype of CD4<sup>+</sup> T-helper (Th) cells, from a Th1 profile, which functions in cell-mediated immune activities, to a Th2 profile, which is involved in antibody production. Studies have shown that stress-induced changes in cytokine balance can lead to the dysregulation of cell-mediated immune responses. Both major and minor stressful events can have direct adverse effects on a variety of immunological mechanisms. Studies on animal models have demonstrated that stress hormones inhibit the trafficking of neutrophils, macrophages, antigen-presenting cells, Natural killer (NK) cells and T and B lymphocytes, suppress the production of proinflammatory cytokines and chemokines, downregulate the production of cytokines necessary for the generation of adaptive immune responses and impair effector functions of macrophages, NK cells, and lymphocytes. Stress can also exacerbate viral and

bacterial pathogenesis, slow wound healing, and alter autoimmune diseases.

Experiments using animal models have advanced the knowledge base on mechanisms and have enabled the investigation of the effect of various stressors on the pathophysiology of infectious agents administered at a variety of anatomical sites. These animal studies have shown that stress diminishes vaccine responses, exacerbates viral and bacterial pathogenesis, slows wound healing, and alters autoimmune diseases. Such studies are not possible in humans due to practical and ethical limitations.

Although more than 150 clinical studies have shown that stress can alter immune function and contribute to poor health, human studies have a limited ability to show a direct connection owing to practical and ethical limitations. However, data from both human and animal studies show that the connections between the neuroendocrine system and the immune system provide a finely tuned regulatory system required for health. Disturbances at any level of the stress response can lead to an imbalance in the physiology of the body and can lead to enhanced susceptibility to infectious diseases. Therefore, it is essential to understand the mechanisms of stress-associated immune dysregulation, which can lead to the development of effective interventions for the prevention and treatment of infectious diseases.

## LITERATURE REVIEW

### HPA Hub and Glucocorticoid Chemicals

The hypothalamus, which is responsible for receiving and monitoring information about the environment, plays a vital role in coordinating responses through a complex system of nerves and hormones. It is activated by various sensory inputs, such as visual information, smell, hearing, temperature sensation, and pain, which alert it to emergencies or environmental hazards. In addition, the emotional portions of the brain also relay information to the hypothalamus [1,2].

As an integrative center, the hypothalamus controls hormone secretion from various glands, including the pituitary gland and the adrenal glands. For instance, the corticotrophin-releasing hormone is secreted from the paraventricular nucleus of the hypothalamus into the hypophyseal portal blood supply, which subsequently stimulates the expression of Adrenocorticotropic Hormone (ACTH) in the anterior pituitary gland. ACTH then circulates in the bloodstream to the adrenal glands, where it induces the expression and release of Glucocorticoid (GC) hormones [3,4].

The GC hormones produced in response to stress affect cardiovascular and renal function, metabolism, and the nervous system, helping to adjust our responses to the environment. They stimulate the metabolism of glucose to provide energy to flee or combat an immediate threat. However, when chronically activated, the Hypothalamic-Pituitary-Adrenal (HPA) axis, which regulates the production of GC hormones, can cause deterioration in general health and worsen existing diseases [5,6].

Since the 1940s and 1950s, GC hormones have been prescribed clinically due to their potent anti-inflammatory properties. The 1950 Nobel Prize in Medicine was awarded to Edward Kendall, Tadeus Reichstein, and Philip Hench for their research on hormones of the adrenal cortex. Over time, it has become increasingly clear that GC hormones also regulate a wide range of immune-cell functions. They modulate cytokine expression, chemoattractant expression, adhesion-molecule expression, immune-cell trafficking, proliferation, differentiation, and effector function [7,8].

Despite much research, the precise mechanism by which GC hormones mediate their wide spectrum of immunological influence remains to be determined. However, significant progress has been made in understanding their mode of action over the past decade or so, providing new insights into this complex process [9,10].

### Mechanisms by which GC hormones work

Glucocorticoid (GC) hormones are lipophilic molecules that can easily pass through the plasma membrane of all cells in the body. If a cell has a GC receptor (GR) or mineralocorticoid receptor (MR), it can be a target for GC hormone action. Corticosterone has a higher affinity for MR than for GR, so at low circulating levels, GC hormones bind preferentially to MR. Only at high circulating or tissue levels (i.e., during stress) is the GR occupied [11].

In immune cells, such as macrophages and T lymphocytes, the primary receptor for GC hormones is GR. The GR is a member of the steroid hormone-receptor superfamily and is structurally divided into three distinct regions: an N-terminal domain involved in transactivation, a middle section called the DNA-binding domain that mediates DNA

binding through two zinc fingers, and a C-terminal domain or ligand-binding domain responsible for ligand binding and involved in transactivation, dimerization, and Heat Shock Protein 90 (HSP90) binding [12,13].

In its inactivated state, the GR is located in the cytoplasm, where it is part of an oligomeric complex containing HSP90 that holds the GR in a conformation that is available to incoming cortisol or corticosterone. On ligand binding, GRs dissociate from this complex and translocate to the nucleus, where they bind as a homodimer to target elements or Glucocorticoid Response Elements (GREs) through zinc fingers of the DNA-binding domain. The bound GR-ligand complexes can then influence gene expression by modulating transcription through several proposed mechanisms [14,15].

As homodimers, GC receptors recognize the putative hormone response element, GAACAnnnTGTTTC (where nnn represents any three bases). However, many of the proteins (cytokines) regulated by GCs do not possess this putative hormone response element. Thus, this simple model for transactivation does not provide the complete answer for GC regulation of cytokine gene expression [16,17].

In 1995, two publications presented data that GC hormones could interfere with NF- $\kappa$ B activity. Specifically, these two studies showed that GC hormones could transactivate an inhibitor of NF- $\kappa$ B activity. The hypothesis is that the GC induces the transcription of I $\kappa$ B $\alpha$ , which then sequesters NF- $\kappa$ B in the cytoplasm and prevents it from translocating to the nucleus and inducing gene activation. This is a logical explanation for the broad spectrum of cytokine suppression mediated by GCs. Many of the cytokines produced by macrophages and by Th cells are under the control of NF- $\kappa$ B; therefore, if GCs could repress activation, then individual cytokines would not need to possess the putative hormone response elements for GCs. Instead, by inhibiting NF- $\kappa$ B transcriptional activity, multiple cytokine genes could be turned off simultaneously [18,19].

However, subsequent publications showed that in some cell types, I $\kappa$ B $\alpha$  synthesis was not necessary for NF- $\kappa$ B inhibition by GCs. Additionally; the anti-GC drug RU486 was also capable of inhibiting NF- $\kappa$ B to some extent. Together, these observations suggest that *de novo* gene transcription induced by GCs is not required for NF- $\kappa$ B inhibition [20,21].

Another model proposes that there is substantial crosstalk between NF- $\kappa$ B and the GR that might prevent gene expression. The activated GC receptor has the capability of binding directly to NF- $\kappa$ B and preventing its transmigration to the nucleus. Also, the activated GC receptor has the capability of binding directly to NF- $\kappa$ B as it is attached to its putative  $\kappa$ B DNA binding locus. In this configuration, the GC receptor prevents the productive assembly of the polymerase complex for gene transcription. The district of the GR expected for the actual constraint of NF- $\kappa$ B, in which the GC prompts I $\kappa$ B amalgamation may be restricted to specific cell types, like monocytes and lymphocytes [22,23].

### **Catecholamines, the Adrenal Medulla, and the Sympathetic Nervous System**

The immune system is regulated not only by glucocorticoid hormones associated with distress but also by catecholamines which modulate various immune functions. Catecholamines act in coordination with the activation of the HPA axis and are produced in the adrenal medulla alongside glucocorticoid hormones. Norepinephrine and epinephrine are synthesized and secreted by cells in the adrenal medulla, with epinephrine accounting for around 80% of the catecholamine output in humans. Norepinephrine is released directly by sympathetic nerve fibers in proximity to target tissues [24,25].

When the body is acutely activated, the catecholaminergic systems provide a necessary "boost" to deal with an immediate threat. This fight or flight reaction is characterized by increased heart rate and increased blood flow to skeletal muscles. However, chronic activation of the sympathetic nervous system and the HPA axis can dysregulate immune function [26,27].

Noradrenergic sympathetic nerve fibers run from the central nervous system to both primary and secondary lymphoid organs, suggesting a link between the sympathetic nervous system and the immune system. Evidence suggests that sympathetic nerve terminals synapse with neighboring immune cells, where they release noradrenaline. Furthermore, epinephrine released from the adrenal medulla travels through the bloodstream and binds to specific adrenergic receptors on immune cells, inducing the same effects as direct sympathetic nervous stimulation [28,29].

### **Mechanism of Action for Catecholamines**

Catecholamines are molecules that mediate their effects on target tissues through adrenergic receptors. These receptors are expressed on numerous cells of the immune system, including lymphocytes and macrophages. Adrenoreceptors are G-protein coupled receptors that can be divided into two subgroups: alpha and beta-adrenergic receptors. Among these receptors, the beta 2-adrenergic receptor is the most important receptor for the immune system [25,26].

Beta-adrenergic receptors function as intermediaries in transmembrane signaling pathways that involve receptors, G-proteins, and effectors. The beta 2-adrenergic receptor is a seven membrane-spanning, serpentine receptor that is embedded in the plasma membranes of many cell types, including macrophages and T lymphocytes. When bound to a ligand, the beta 2-adrenergic receptor communicates with the cytoplasm by stimulating the activation of a G-protein complex [28,27].

This G protein is formed from three distinct protein subunits: alpha, beta, and gamma. When in its inactive form, the three G-protein subunits are bound together in a heterotrimeric complex. In its inactive state, the G-alpha subunit is bound to Guanosine Diphosphate (GDP). When active, it binds the triphosphate form (GTP). When the beta-adrenergic receptor activates the G protein as a result of the binding of a catecholamine, the alpha subunit releases GDP and binds GTP [29,30].

Once this happens, the GTP-bound alpha subunit loses affinity for the receptor and for the beta and gamma subunits, dissociates from them, and subsequently activates adenylate cyclase. In turn, adenylate cyclase catalyzes the synthesis of cAMP from ATP. This reaction involves the release of the beta and gamma phosphates from ATP and the linking of the surviving alpha phosphate (still attached to the 5' hydroxyls of ribose) to the 3' hydroxyls as well, forming cAMP [31,32].

One major cellular effect of the activation of the cAMP cascade is the stimulation of transcription after phosphorylation of transcription factors by cAMP-dependent Protein Kinase A (PKA). One such transcription factor, called CREB (cAMP response element binding protein) binds to the conserved consensus cAMP response element, TGACGTCA, present in the promoter regions of responsive genes [33,34].

CREB stimulates basal transcription of cAMP response element-containing genes and mediates induction of transcription on phosphorylation. For example, a conserved palindromic cAMP response element has been identified in the promoter of various genes regulated by cAMP (i.e. IL-6). After phosphorylation on Ser133 by PKA, CREB binds as a homodimer to this palindromic element and stimulates elevated transcription. As such, the expression of numerous immune response genes can be modified by elevated catecholamine production during times of stress [35,36].

### **CONCLUSION**

The primary focus of this review has been on the impact of GC hormones and catecholamines on immune responses in response to stress. However, it is important to note that there are likely other physiological pathways involved in this complex interplay. Recent studies have shown that endogenous opioids can reduce the cytotoxicity of natural killer cells, while neuropeptides like substance P can suppress inflammatory responses by reducing IL-16 production by eosinophils.

While the anti-inflammatory effects of GC hormones are mainly associated with inhibiting NF- $\kappa$ B, the Glucocorticoid Receptor (GR) likely interferes with the function of other transcriptional regulators as well. Studies suggest that protein-protein interactions similar to those observed for GR-NF- $\kappa$ B are also involved in the GC inhibition of Activator Protein-1 (AP-1) and nuclear factor of activated T lymphocytes (NF-AT). What is interesting is that each of these limitations shows a strong connection among the immune, nervous, and endocrine systems.

New data continue to emerge, providing greater insight into the mechanisms that govern the interplay between these three body systems. It is now widely accepted that stressful life events can have a significant impact on an individual's health, including their immune system health. Although there is still much to be learned about the specific details of this complex interplay, it is becoming increasingly clear that products of the endocrine system, such as GC hormones, and products of the nervous system, such as catecholamines, can significantly alter the function of macrophages, lymphocytes, and other cells of the immune system.

## DECLARATIONS

## Conflict of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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