

Interactive Functional Specificity of the Stress and Immune Responses: The Ying, the Yang, and the Defense against 2 Major Classes of Bacteria

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(See the article by Straub et al., on pages 560–72.)

The stress and immune systems play crucial roles in maintaining homeostasis [1, 2]. The former is relatively nonspecific, in the sense that it is activated by any threat to general homeostasis—including immune threats, when that threat exceeds a certain threshold—whereas the latter is relatively specific, in the sense that it is primarily activated when injurious agents come into contact with the tissues of the organism. During the past few decades, it has become apparent that the stress and immune systems extensively interact with each other, influencing each other's activity, with the purpose of the successful defense against and adaptation of the organism to injurious agents. The study by Straub et al. [3] in this issue of the *Journal of Infectious Diseases* examines and eloquently describes the interaction of the stress and immune systems with regard to the powerful influence of the stress system on the quality of the defense of the

organism against gram-negative versus gram-positive bacteria. This study highlights several key concepts that pertain to the interaction of these 2 systems that are important to review.

THE STRESS SYSTEM AND THE SYSTEMIC STRESS RESPONSE

Mammals survive threats to homeostasis—or stressors—by a concerted adjustment of several biological/physiological functions that, together, lead to behavioral and physical adaptation to the stressful situation [1, 2]. The stress response is coordinated and mediated by the centers of the stress system in the brain, along with their respective peripheral limbs (figure 1A). The centers in the brain consist of the hypothalamic corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) neurons of the paraventricular nuclei (PVN) and the brainstem noradrenergic neurons of the locus caeruleus/nor-epinephrine (LC/NE)—central sympathetic systems. The peripheral limbs include the hypothalamic-pituitary-adrenal axis and the systemic sympathetic and adrenomedullary nervous systems. The central components of the stress system innervate and

stimulate each other, participating in a positive, reverberatory feedback loop, with PVN CRH- and AVP-secreting neurons stimulating the brainstem LC/NE neurons and vice versa.

Activation of the central stress system leads to the secretion of CRH and AVP into the hypophysial portal system and, hence, to the stimulation of pituitary adrenocorticotrophic hormone and adrenocortical glucocorticoid secretion. This activation also leads to the stimulation of the systemic sympathetic and adrenomedullary nervous systems and, thus, to the peripheral secretion of NE, epinephrine, and several neuropeptides, such as immune CRH [4, 5].

The stress system receives input from and responds to the environment, the inner self, and the internal milieu of the body [1, 2]. It receives information neurally from the sensory organs, the areas of the brain that generate emotions, the neural afferent fibers of the autonomic nervous system, and the neural somatosensory afferent fibers; it also receives information humorally through the circulation, from injurious agents or signal-carrying molecules—such as hormones, growth factors, neurotransmitters, neuropeptides, cytokines, and other mediators of inflammation.

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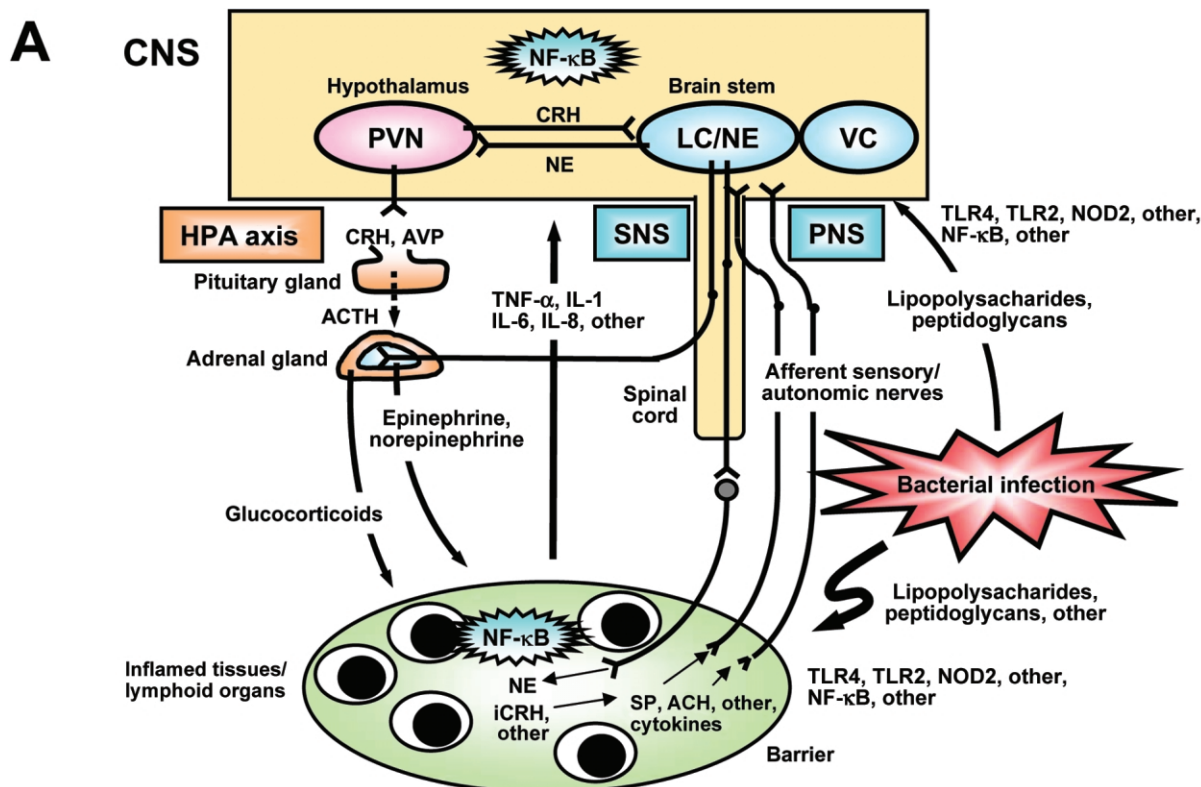


Figure 1. A, Interactions between the stress system—composed of the hypothalamic-pituitary-adrenal (HPA) axis and the locus caeruleus/norepinephrine (LC/NE) sympathetic and parasympathetic systems—and an immune and inflammatory response during a bacterial infection. Bacterial cell-wall products, such as lipopolysaccharides (gram-negative) or peptidoglycans (gram-positive), activate immune and immune-related cells at peripheral and central nervous system sites through specific receptors on the plasma membrane or in the cytoplasm, such as Toll-like receptor (TLR) 4 (a membrane pattern recognition receptor) in gram-negative or TLR2 and nucleotide-binding oligomerization domain—intracellular pattern recognition receptor (NOD2; also called “CARD15”) in gram-positive infection, respectively. These receptors turn on specific intracellular kinases that activate proinflammatory transcription factors, such as NF- κ B, that stimulate the innate immune system, leading to the production of inflammatory cytokines and other mediators of inflammation, such as eicosanoids, platelet activation factor, nitric oxide, oxygen, and tissue-degrading enzymes. Proinflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6, the chemokine IL-8, and others, stimulate the stress system, whose products—e.g., NE, epinephrine, acetylcholine, glucocorticoids, immune corticotropin-releasing hormone (iCRH), and urocortin—influence the innate and adaptive immune response in several ways. The stress system participates in the regulation of the entire innate immune response. Thus, iCRH from postganglionic sympathetic nerves activates mast cells, whose products are among the first to initiate the process of inflammation. On the other hand, acetylcholine secreted from parasympathetic terminals is one of the earliest anti-inflammatory reflexes. In a different mechanism, NE and epinephrine from the sympathetic nerve terminals and the adrenal medulla exert primarily anti-inflammatory effects by respectively inhibiting and stimulating the production of the Th1- and Th2-type cytokines. Glucocorticoids from the adrenal cortex have a similar overall effect on the polarization of the innate and adaptive immune response toward an “anti-inflammatory” and humoral phenotype. B, Stimulation of an innate inflammatory response by tissue injury and bacterial entry that is initially predominately proinflammatory and later predominately “anti-inflammatory” (but both subserve defense). It appears that the former and latter are protective against gram-negative and gram-positive bacteria, respectively. ACTH, adrenocorticotropic hormone; AVP, arginine-vasopressin, CARS, counterregulatory response syndrome; MODS, multiple-organ dysfunction syndrome; PNS, parasympathetic nervous system; PVN, paraventricular nucleus; SIRS, systemic inflammatory response syndrome; SP, substance P; SNS, sympathetic nervous system; VC, vagal complex.

THE IMMUNE SYSTEM AND THE LOCAL AND SYSTEMIC IMMUNE RESPONSE

The immune system is responsible for defense against different injurious agents, including foreign molecules from different

kinds of microorganisms, intracellular host molecules released during cell necrosis, and host denatured or oxidized molecules. The immune or inflammatory response is activated by such injurious agents through several classes of recognition molecules or receptors. This response can be local and limited or sys-

temic, spanning a wide range of clinical and biochemical manifestations. The biological programs that unfold during a systemic immune response and inflammation are heuristically called “the sickness syndrome,” which is divided into sickness behavior, the acute-phase reaction, and the pain and fatigue system re-

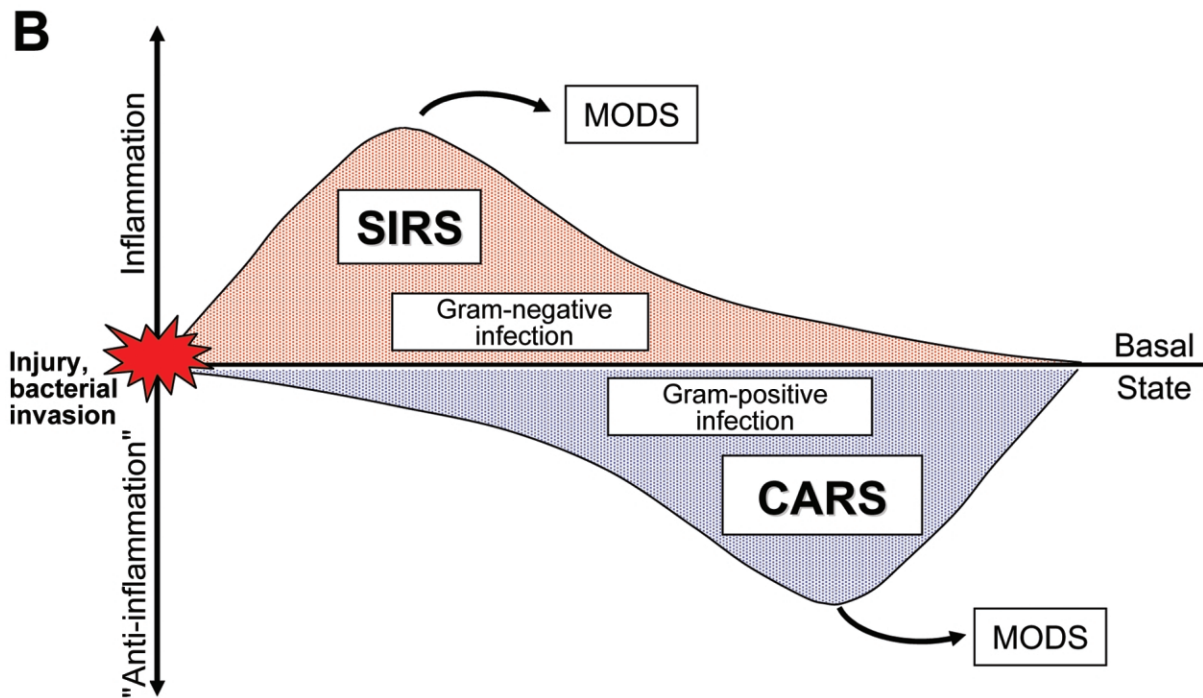


Figure 1. (Continued.)

action (table 1) [4]. Once the magnitude of the immune response exceeds a certain threshold, activation of the stress response also occurs, with effects that antagonize or potentiate those of the immune response (table 1). Although we have traditionally characterized the stress response as either anti-inflammatory or immunosuppressive, this categorization is not entirely accurate, and it should not be thought to indicate that it is anti-inflammatory [5, 6].

Indeed, the immune or inflammatory response is an integrated defense reaction of the organism that includes the inflammatory reaction, which has been divided into a pro- and an “anti-inflammatory” response (figure 1B). The proinflammatory versus the anti-inflammatory immune response, however, are the tandem ying and yang of the defense response, with the yang (the anti-inflammatory response) being crucial in returning the organism to its baseline homeostasis. Despite their different polarity and apparently opposing effects, both components of the defense response—pro- and anti-

inflammatory—are defensive against injurious agents in their own right, as is evident in the study by Straub et al. [3]. Thus, proinflammatory activity and an efficient defense response are not synonymous or equivalent.

The parasympathetic nervous system is often not considered in the regulation of the stress and immune responses [1]. Acetylcholine secreted by the parasympathetic nerve terminals, however, like the catecholamines and the glucocorticoids, also has potent suppressive effects on the innate proinflammatory response, converting it into an anti-inflammatory response [7].

DETERMINANTS OF IMMUNE SPECIFICITY

There are many factors that determine the specificity of an immune response. The type of tissue or organ affected, the location of the inflamed site in the body, the presence of local barriers (e.g., the peritoneum, meninges, blood-brain barrier, and synovium), the presence of local im-

mune-related cells (e.g., mast, dendritic, and endothelial cells), the attraction of distant immune cells to the inflamed site, the biochemical or humoral microenvironment, and the endocrine and nervous systems all affect the type, degree, and specificity of inflammation. Recently, it has also become apparent that there are target tissue cellular factors that influence the specificity of an immune reaction of both classes and individual cells of a different or same lineage [7–9].

The functional specificity of our defensive immune response toward specific injurious agents is thus determined by a large number of molecules in the plasma membrane and cytoplasm. For example, NF- κ B, when not stimulated, is located in the cytoplasm and is kept inactive in complex with other molecules [7, 9]. A myriad of injurious agents and cytokines can stimulate NF- κ B, causing its translocation into the cell nucleus, where it interacts with the promoters of genes related to inflammation, either directly with specific response elements or through other transcription factors that regulate the ex-

Table 1. Unfolding of major biological programs during the immune response.

Sickness syndrome (acute-phase reaction, sickness behavior, pain, and fatigue response)	Classic stress syndrome
Anorexia/nausea	Anorexia/stimulation of appetite ^a
Fatigue and/or depressed affect	Motivation/stimulated affect
Somnolence	Arousal
Hyperalgesia ± headache	Analgesia
Elevated temperature/fever	Pyretic/antipyretic ^a
Increased metabolic rate	Increased metabolic rate/return to normal ^a
Acute-phase reaction +++++	Acute-phase reaction +
Cellular effectors	
Immune and immune-related cells, neurons, endocrine cells	Neurons, endocrine cells, immune and immune-related cells
Molecular effectors	
Inflammatory cytokines/mediators, immune CRH	CRH, AVP, glucocorticoids, catecholamines, immune CRH, acetylcholine
Transcription factors: GR, NF-κB, CREB, AP1, STATs	Transcription factors: GR, NF-κB, CREB, AP1, STATs

NOTE. Modified with permission from *Annals of the New York Academy of Sciences* [4]. AP1, activating protein 1; AVP, arginine-vasopressin; CREB, cAMP response element-binding protein; GR, glucocorticoid receptor; STAT, signal transducer and activator of transcription; +, 1–5 degrees of activation.

^a Initial stimulation via corticotropin-releasing hormone (CRH) and catecholamines, then inhibition by glucocorticoids.

pression of proteins—such as the glucocorticoid receptor—that influence inflammation [10]. In the cell, there are 2 major signaling pathways of NF-κB activation—canonical and noncanonical—and there are at least 5 NF-κB signalosomes that can be formed: those formed after the specific activation of Toll-like receptors (TLRs), tumor necrosis factor-α superfamily receptors, NK cell receptors, T cell receptors, and B cell receptors [9]. Thus, immune or immune-related cell activation results from a highly stochastic, integrative process.

Pertinent to the study by Straub et al. [3], there is known functional specificity of the NF-κB signaling system for gram-positive versus gram-negative bacteria. Thus, membrane TLR2 and the intracellular pattern recognition receptor nucleotide-binding oligomerization domain—intracellular pattern recognition receptor (NOD2) bind to and are activated by peptidoglycans, the cell-wall constituent of gram-positive bacteria, whereas membrane TLR4 binds and responds to lipopolysaccharides, the cell-wall constituent of gram-negative bacteria. Interestingly, TLR2 mutations have been associated with susceptibility to infection by *Staphylococcus aureus*, NOD2 mutations with susceptibility to Crohn disease, and TLR4 mutations with susceptibility to gram-negative septic shock, infection by

Neisseria meningitidis, severe respiratory syncytial virus bronchiolitis, and premature birth [9].

In the light of the above findings, it is not surprising that there are differences in the immune response against gram-negative and gram-positive bacteria, with the proinflammatory response protecting the organism against the former and the “anti-inflammatory” response protecting the organism against the latter. The activity of the stress response would then be expected to suppress the proinflammatory response and to stimulate the anti-inflammatory response, with possibly differing effects on overall host defense against the different pathogen types.

Data from rodent models clearly indicate that the proinflammatory response protects against gram-negative bacteria and that the “anti-inflammatory” response protects against gram-positive bacteria. The stress system, by inhibiting the proinflammatory response and by stimulating the “anti-inflammatory” response, compromises an organism’s ability to fight gram-negative bacteria but aids in the fight against gram-positive bacteria. What could be the etiology and the teleology of such a phenomenon? Why has this specificity been genetically selected? What has the genetic advantage been? Are gram-negative bacteria, with

their thin cell walls, easier to kill, and humans have adapted such that they are eliminated as soon as the body is invaded? Is the opposite true for gram-positive bacteria, which may require more time and different defensive strategies to eliminate because of their thick cell walls? Do the potentially lethal exotoxins of gram-positive bacteria require a more humoral immune response phenotype to be neutralized? Are these phenomena also pertinent for humans? Some of these hypotheses are eminently testable with today’s powerful tools of biomedical science.

References

1. Chrousos GP, Gold PW. The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. *JAMA* **1992**; 267:1244–52.
2. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* **1995**; 332:1351–62.
3. Straub RH, Pongratz G, Weidler C, et al. Ablation of the sympathetic nervous system decreases gram-negative and increases gram-positive bacterial dissemination: key roles for tumor necrosis factor/phagocytes and interleukin-4/lymphocytes. *J Infect Dis* **2005**; 192: 560–72 (in this issue).
4. Chrousos GP. The stress response and immune function: clinical implications. The 1999 Novera H. Spector Lecture. *Ann NY Acad Sci* **2000**; 917:38–67.

5. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* **2000**; 52: 595–638.
6. Tracey K. The inflammatory reflex. *Nature* **2002**; 420:853–9.
7. Franchimont D, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH Clinical Staff Conference. *Neuroimmunomodulation* **2002–2003**; 10:247–60.
8. Meduri GU, Tolley EA, Chrousos GP, Stentz F. Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving ARDS: evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. *Am J Resp Crit Care Med* **2002**; 165:983–91.
9. Orange JS, Levy O, Geha RS. Human disease resulting from gene mutations that interfere with appropriate nuclear factor κ B activation. *Immunol Rev* **2005**; 203:21–37.
10. Charmandari E, Kino T, Chrousos G. Glucocorticoids and their actions: an introduction. *Ann NY Acad Sci* **2004**; 1024:1–8.