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In Theory

Is Severe Sepsis a Neuroendocrine Disease?

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> Turning and turning in the widening gyre
> The falcon cannot hear the falconer;
> Things fall apart; the center cannot hold;
> Mere anarchy is loosed upon the world.
>
> *W.B. Yeats*
> from "The Second Coming," *Collected Poems*,
> MacMillan Co., 1924

Introduction

Evolution has endowed vertebrates with two systems for the rapid recognition of threats and mobilization of host defenses. The central nervous system (CNS) detects macroscopic threats to survival, like the sight of a charging lion or the hiss of a rattlesnake, and activates physiologic "fight or flight" responses. The innate immune system detects the presence of microscopic threats, such as invading microbes, and mobilizes cellular and humoral forces to defend against invasion. Ultimately, these neurologic and immune responses also enhance survivability for similar future events, because neurologic memory of the event enables avoidance behavior, and adaptive immunity confers protection against subsequent infection with the same or similar microorganisms. Injury to either defensive system threatens survival. CNS impairment renders mammals unable to defend themselves against bodily attack; similarly, diminishing the innate immune response increases mortality from infection.

It is thus not surprising that these two critical defensive and memory-producing systems are functionally connected or that these connections are important in both health and disease. In this article, we first review how these networks normally cooperate to enhance antimicrobial host defense and regulate local inflammation. We then discuss the possibility that CNS dysfunction contributes to the pathogenesis of severe sepsis, a common and often lethal condition in which the function of multiple organs fails during the systemic response to infection.

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Afferent Communication: Immune System to CNS

Bidirectional communication between the immune system and the CNS optimizes the effectiveness of each system (1,2). Afferent signals, reaching the CNS via the bloodstream and nerves, provide the brain with constantly changing information about the inflammatory response to infection in local tissues. One example of the humoral interaction is interleukin-6 (IL-6), a cytokine that functions as an activator of the hypothalamic–pituitary–adrenal axis and acute phase responses during stress. Like IL-1β, tumor necrosis factor (TNF), and other cytokines, it is also a potent pyrogen that can interact with hypothalamic centers to induce fever (3). Even more sensitive and rapid signaling to the brain can involve neural interactions, as occurs, for instance, via afferent vagus nerve pathways. The diffuse innervation of all organs by the vagus nerve provides a route for the efficient transmission of information from inflamed local tissues to the CNS. Intraperitoneal or intravenous injection of relatively small amounts of IL-1β, endotoxin, and presumably other inflammatory molecules can induce fever by stimulating afferent activity in the vagus nerve (4). This vagus nerve-dependent signaling occurs at response thresholds that are significantly lower than those

necessary to activate febrile responses through elevated humoral levels of the classical "endogenous pyrogens" mentioned. Peripheral sensory nerve fibers can also inform the CNS about the status of peripheral inflammation. Inflammatory mediators elicit potent pain responses when applied to local tissues; pain, a cardinal feature of local inflammation, is transmitted to the CNS through neural networks that can activate anti-inflammatory systemic effects. For example, unilateral stimulation of pain fibers in the foot diminishes inflammation in the contralateral knee through activation of the spinal–hypothalamic–pituitary–adrenal axis (5) and release of L-selectin from circulating leukocytes (6). Together, these observations implicate the local release of inflammatory mediators as a proximal step that, via the humoral route or through at least two distinct afferent pathways (vagus nerve and nociceptive fibers), can in turn activate efferent CNS responses.

Efferent Communication: From the CNS to the Peripheral Immune System

There are at least three major mechanisms through which efferent signals from the CNS can directly modulate peripheral immune responses: 1) the release of hypothalamic–pituitary hormones and cytokines; 2) the activation of the sympathetic nervous system; and 3) via the cholinergic anti-inflammatory pathway. In the first case, pituitary release of ACTH and α-MSH can effectively inhibit activation of innate immune cells and suppress cytokine production, in part by augmenting levels of IL-10 (7). In the second, the sympathetic efferent ("flight or fight") response elevates systemic levels of catabolic "stress" hormones (e.g., glucocorticoids and catecholamines) that directly modulate the responsiveness of immune cells. High circulating levels of catecholamines and cortisol promote demargination of neutrophils within the vasculature, freeing them to travel to local infection sites and reducing the likelihood that they will accumulate in uninflamed tissues. In addition, glucocorticoids and epinephrine inhibit the production of TNF, IL-1β, and IL-12 by stimulated monocytes and they enhance the production of anti-inflammatory molecules such as IL-6, IL-10, and many acute phase proteins (8,9). In the cholinergic anti-inflammatory pathway, increased efferent activity in the parasympathetic system leads to the local release of acetylcholine, a neurotransmitter that interacts with high-affinity macrophage receptors to inhibit the release of TNF and other proinflammatory cytokines (10). The cholinergic anti-inflammatory pathway is a neural-based system through which the CNS can rapidly and efficiently shut down the activation of resident macrophages in the reticuloendothelial system. Vagotomy significantly increases the sensitivity of animals to endotoxin because the normally suppressive, down-regulating effects of the cholinergic pathway are lost and systemic TNF release is significantly enhanced (9). In addition to delivering acetylcholine in peripheral tissues, the vagus nerve is also an important source of vasoactive intestinal polypeptide, an anti-inflammatory neuropeptide (11). In summary, the CNS-derived hypothalamic–pituitary, sympathetic, and parasympathetic responses are specifically positioned to modulate local inflammation, maximizing defensive capabilities while simultaneously preventing systemic toxicity (12).

Whereas these observations support the hypothesis that that circulating CNS-derived mediators exert predominantly anti-inflammatory actions, caution must be noted, because some of the same mediators function to increase extravasation of plasma fluid, enhance leukocyte infiltration, and elicit other pro-inflammatory effects when released into local sites. Catecholamines attenuate the production of cytokines by blood leukocytes, but their effects on tissue macrophages are more complex (9) and may be at least transiently pro-inflammatory. Indeed, the severity of experimental arthritis can be reduced by surgical or pharmacologic sympathectomy (13). In rodents, a neural reflex mediates the ability of inflammation in one joint to provoke swelling and lymphocytic infiltration in the contralateral joint; although not much is known about this reflex, the efferent limb is dependent upon sympathetic terminals and local release of prostaglandins (14). Context-dependent action is not limited to CNS-derived mediators. In addition to corticotropin-releasing hormone, β-endorphin, and catecholamines, there is evidence that prostaglandin E_2, IL-6, C3desArg, and IL-10 may be pro-inflammatory in local sites but anti-inflammatory in the circulating blood. These and other studies support the concept that both local inflammation and systemic anti-inflammation are necessary for effective, nonlethal immune system-mediated defense against infection or injury (15).

Efferent CNS Pathways in Regulation of the Hepatic Acute Phase Response

The liver occupies a critical regulatory role in the systemic response to infection, in part because it is the major source of both acute phase proteins and circulating TNF. The liver is richly innervated by the vagus nerve, and the production of both acute phase proteins (which seem to serve anti-infective and/or anti-inflammatory functions [12,16]) and TNF (a potentially toxic pro-inflammatory cytokine) is responsive to CNS signals. For instance, small quantities of endotoxin, IL-1, or TNF in the cerebrospinal fluid stimulate increases in systemic IL-6 levels, and this pathway drives enhanced hepatic acute phase protein (APP) production (17,18). Increased IL-1 production in the brain also results in significantly increased serum IL-6 levels, which in turn enhance the acute phase response (18). As noted, the liver is a major source of the TNF found

in the blood in response to severe infection, and hepatic TNF production is significantly attenuated by increased efferent activity in the vagus nerve (10).

It is interesting to consider how microbial invasion of the liver might trigger an orchestrated interaction between the peripheral immune system and the CNS. The presence of microbial products (e.g., LPS) in liver activates a local, Kupffer cell-dependent inflammatory response. Information about the status of this innate immune activation is simultaneously transmitted to the brain through hepatic branches of the vagus nerve. These ascending pathways converge in the hypothalamus and brainstem, activating the three major CNS-derived anti-inflammatory pathways, discussed above, that counter-regulate TNF release. Thus, a local inflammatory response to infection stimulates CNS-dependent neural and humoral pathways that inhibit local macrophage activation and TNF release, preventing potentially toxic inflammatory products from spilling into the systemic circulation. Concomitantly, CNS-derived mediators initiate or amplify the production of APPs and other anti-inflammatory molecules; especially important in this context may be catecholamine-enhanced production of IL-6 (19), the major activator of the acute phase response, and of IL-10, a potent anti-inflammatory cytokine (20). Together, these responses should support the low-level inflammatory response in liver, yet restrain the synthesis or movement of inflammatory mediators to prevent inappropriate systemic release.

Failure to Control Inflammation: Severe Sepsis

Severe sepsis is a pathologic state in which organs distant from a site of infection do not function normally. Although pulmonary dysfunction (acute respiratory distress syndrome) is most common, hepatic dysfunction, renal failure, CNS derangements, and cardiovascular dysfunction also occur. In numerous recent studies, patients who developed severe sepsis or septic shock have had case-fatality rates of 25–50%. Most explanations for the pathogenesis of severe sepsis and septic shock have invoked the excessive production of cytokines and other mediators, endothelial dysfunction, and microvascular thrombosis (21). Recent evidence suggests that these phenomena may occur most often when systemic forces fail to control local inflammation. In an experimental model of *Pseudomonas aeruginosa* pneumonia in rabbits, for example, septic shock only developed when the alveolar epithelium was injured and inflammatory mediators could enter the blood; bacteremia, even with large concentrations of circulating organisms, did not induce shock (22). Similarly, a large study of bacteremic patients found that the risk of severe sepsis was related to the tissue site at which the infection originated—bacteremia from a CNS, pulmonary, or abdominal source was much more likely to be associated with severe sepsis than was bacteremia originating from an infected catheter or in the urinary tract (23). The nature of the bacterial isolate was less important than the site of primary infection, again suggesting that some feature of the local inflammation was the critical determinant. Other studies have found that patients with severe sepsis and patients who have sustained major trauma have similar profiles of circulating anti-inflammatory mediators. In contrast, only patients with severe sepsis have high blood levels of TNF, MIF, HMG-1, and other pro-inflammatory molecules (24). Procoagulant changes are also detectable in post-trauma patients, but the occurrence of disseminated intravascular coagulopathy is significantly more common in patients with severe sepsis. Taken together, these observations suggest that severe sepsis occurs after pro-inflammatory mediators move from an infected local site into the circulating blood, exacerbate coagulopathy, and induce functional changes in distant organs. In other patients, these phenomena may be elicited within the bloodstream by intravascular pathogens such as *Neisseria meningitidis*. Remarkably, it appears that these changes can occur when the blood contains both high concentrations of numerous anti-inflammatory molecules and leukocytes that have been reprogrammed to diminish their production of pro-inflammatory mediators (25–27).

As noted, there is strong evidence that the CNS controls many of the body's systemic responses to infection and injury. It is thus reasonable to ask whether the maximal expression of these responses, as often occurs following trauma or during critical illness, leads to immunosuppression and increases the risk of infection by commensal microbes (12,20). Is it also possible that inadequate neuroendocrine regulation of the inflammatory response at a site of infection contributes to the pathogenesis of severe sepsis?

CNS Dysfunction in Severe Sepsis

The onset of severe sepsis is frequently accompanied by overt CNS dysfunction. Common manifestations include confusion, delirium, weakness, autonomic dysregulation, hypothalamic–pituitary dysfunction, accelerated resting energy expenditure, and/or abnormalities in the normal feedback loops that influence the humoral and neural output of the CNS. Loss of hypothalamic sensitivity to corticotropin-releasing hormone affects feedback control of the hypothalamic–pituitary–adrenal axis (28), and decreases in pituitary vasopressin release can contribute to hypotension (29). The normally pulsatile pattern of growth hormone release is maintained but the pulses lose amplitude (30,31). Circadian variation in the blood concentrations of cortisol, IL-6, growth hormone, and leptin disappears. Hypothermia, noted in approximately 10% of severely septic patients, may reflect dysfunction of thermoregulatory control centers. Abnormalities in sympathetic/parasympathetic

balance may be revealed by changes in heart rate variability; at least in neonates, these changes can precede the onset of severe sepsis (32,33). Autonomic insufficiency is also suggested by a lack of baroreflex-mediated bradycardia after vasopressin infusion (29).

There is recent evidence that, in septic patients, CNS function correlates with prognosis. In one large clinical trial, the case-fatality rate of septic patients with mildly abnormal mental status was twice that of patients whose mental status was considered normal (34). Other studies have found that hypothermia nearly triples the risk of dying from severe sepsis (35) and that loss of heart rate variability, a reflection of central autonomic dysregulation, is also associated with increased mortality (36).

CNS dysfunction might contribute to the pathogenesis of severe sepsis through at least two mechanisms. First, impairment of neural-based pathways for interorgan communication between the hypothalamus or brainstem and target organs can interrupt normal central–peripheral signaling. Dysfunction of these neural networks during sepsis is manifested by abnormal baroreflexes and by an uncoupling of the biological oscillations in heart rate, blood pressure, respiration, and other functions that are normally connected through functional neural networks (37,38). To complicate this further, the plasma compartment of the septic patient contains abnormal concentrations of more than 50 molecules; when faced with such an array of abnormal signal information, cells might lose their ability to sense their environment and respond normally. Disruption of normal pathways for interorgan and intercellular communication could contribute to a loss of physiologic complexity that, as suggested by others, may be a fundamental cause of multiple organ dysfunction (37,39).

In a second potential mechanism, diminution of CNS-mediated anti-inflammatory mechanisms would favor the overproduction of inflammatory mediators at local sites. Efferent, inflammation-suppressing output from the CNS might be rendered insufficient to prevent systemic inflammation in several ways. There could be inadequate stimulation of afferent CNS pathways by immune mediators, for example, perhaps akin to immune "sensory deprivation"; the available evidence does not address this possibility. Alternatively, the output of the CNS through humoral or neural efferent pathways might be inadequate to control inflammation. Here the data are somewhat conflicting. Reduced cortisol responses to CRH stimulation have been found in nonsurvivors of severe sepsis (28), yet the highest blood levels of anti-inflammatory mediators ever reported have been from septic patients. Moreover, several groups of investigators have found that plasma from septic patients inhibits the responses of naïve reporter cells to endotoxin (38), suggesting a net anti-inflammatory effect even after TNF and other pro-inflammatory molecules have entered the blood. On the other hand, in the rabbit model of *P. aeruginosa* pneumonia mentioned above, intravenous administration of recombinant IL-10 improved both bacteremia and septic shock (22), suggesting that higher levels of this and/or other anti-inflammatory mediators might enhance local immunity and prevent systemic complications.

The available evidence most strongly suggests that inadequate responsiveness to CNS-derived signals is caused by peripheral desensitization or tachyphylaxis. First, the pressor response to a given dose of norepinephrine is usually subnormal in patients with septic shock (40). The abnormal pressor response may be due to down-regulation of vascular endothelial and smooth muscle cell responsiveness to catecholamines (41). Normalization of the pressor response by the administration of hydrocortisone may reflect a glucocorticoid-mediated increase in adrenergic receptor expression and sensitivity to cAMP (9). Second, just as the ability of epinephrine to augment LPS-induced IL-10 production in normal human volunteers is impaired after prolonged epinephrine infusion (8), there is evidence that a critical step in this process, the stimulation of cAMP production by circulating leukocytes, is reduced in blood obtained from septic patients; diminution of IL-10 production would thus be expected (42). Third, because acute administration of catecholamines increases, and chronic administration decreases, the number of natural killer cells in the blood (9), it is possible that the inability of some septic individuals to mount a neutrophilic leukocytosis in the peripheral blood is due to failure of catecholamines and/or cortisol to inhibit neutrophil–endothelial adhesion. In summary, desensitization to the effects of catecholamines and/or glucocorticoids may contribute both to an inadequate anti-inflammatory systemic response and to the development of organ dysfunction and septic shock. The phenomenon of tachyphylaxis or desensitization can also apply to pro-inflammatory mediators, even to TNF (43). Although desensitization to the effects of acetylcholine and other neuroendocrine mediators has received less study, it is reasonable to consider that cells from septic patients may have diminished responsiveness to these and other agonists that normally modulate or suppress pro-inflammatory cytokine synthesis.

Similar considerations may be readily extended to the so-called "second hit" phenomenon. The clinical course of post-trauma patients is frequently characterized by an initial, severe infection (e.g., perforated viscus) that activates a robust inflammatory response. Most patients survive this episode, but some subsequently acquire a modest, less severe infection (e.g., an infected intravenous catheter site) that is complicated by the development of a severe, protracted, and lethal sepsis syndrome. Together, the observations reviewed here raise the possibility that CNS responses to the second infection ("hit") are insufficient to suppress the spread of inflammation from the local site into the systemic milieu. The

ineffective response might be due to target cell desensitization or to depletion of neurotransmitters and hormones.

Is Severe Sepsis a Neuroendocrine Disease?

The available scientific data do not provide a convincing answer to this question, but one may consider several ways to test the hypothesis that CNS dysfunction precedes or underlies the development of severe sepsis. It may be possible to develop animal models of sepsis that allow one to perform classic CNS lesioning studies to identify pathways that significantly enhance susceptibility to lethality, or that convert a localized, minor infectious challenge into a systemic infection. Pharmacologic studies can also be performed in such models to test the impact of agonists and antagonists of specific neurotransmitters. Human studies raise additional challenges, as always, but the number of patients with implanted vagus nerve stimulators is increasing, and if such patients were to develop infection or sepsis, it should be possible to test the impact of stimulating the vagus nerve on the course of sepsis and the magnitude of the inflammatory response. Nicotine patches, which have been used to therapeutic advantage in the treatment of ulcerative colitis, might also be studied in patients at risk of developing sepsis, because the cholinergic anti-inflammatory pathway functions by signaling through nicotinic receptors on macrophages. Desensitization of peripheral blood cells to neuroendocrine agonists other than catecholamines and glucocorticoids can be studied ex vivo using blood from septic patients and normal controls. Finally, prospective studies could be performed to monitor CNS outflow and activity (EEG, autonomic tone, neuroendocrine function) in an effort to define whether measurable CNS dysfunction precedes the onset of severe sepsis. In addition to providing supportive evidence for the hypothesis raised here, identifying such an anticipatory event or marker might make it possible to forestall the septic process before multiple organ dysfunction occurs.

There is no doubt that CNS dysfunction is a frequent complication of severe sepsis; the question being considered here is whether CNS dysfunction has a causal role in the pathobiology of the complete clinical syndrome of sepsis. It may be extremely difficult to sort out the specific aspects of CNS dysfunction that contribute to the development of severe sepsis, but it is nonetheless intriguing that local tissue cytokine production can be significantly increased by denervation of an organ (9). The available evidence is consistent with the possibility that failure of CNS-derived, inflammation-suppressing mechanisms either permits the development of severe sepsis or is necessary for the full expression of the syndrome. By raising the question here of whether neurologic dysregulation itself underlies the inappropriate, and potentially injurious, overexpression of inflammatory products that mediate severe sepsis, we hope to provoke direct consideration of this possibility. Studies of this potentially controversial hypothesis may well lead to improved understanding of the pathogenesis of severe sepsis and septic shock, and lay the basis for the development of future diagnostics and therapeutics.

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