

Inflammation at the Intersection of Behavior and Somatic Symptoms

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KEYWORDS

- Fatigue • Sleep • Pain • Sickness behavior • Inflammation
- Somatization

Somatization refers to the persistence of multiple physical complaints that cannot be attributed to a medical illness. Increasing evidence suggests that activation of the proinflammatory cytokine network can lead to a constellation of behaviors, “sickness behavior,” which might underlie the pathophysiology of certain psychiatric disorders.^{1,2} In particular, depressive disorders, as well as somatoform disorders, share many components of “sickness behavior,” including alterations in pain sensitivity such as exaggerated pain response (hyperalgesia), sleep disturbance, and fatigue.³ It has recently been hypothesized that this overlap in symptoms between somatoform disorders and depression may be due to a common underlying biology, including activation of inflammatory biology dynamics.^{3,4} In this review, we characterize inflammation, describe the connections between the immune system and the brain, and discuss the influence of proinflammatory cytokine activity on certain aspects of this constellation of behaviors that have been commonly referred to as “sickness behavior.” In particular, we focus on 3 prominent behavioral complaints in somatic disorders: exaggerated pain sensitivity (hyperalgesia), sleep disturbance, and fatigue.⁵ Within this conceptual frame linking inflammation with altered bodily perceptions, we consider the possibility that activation of proinflammatory cytokines, possibly acting in concert with stress, might lead to increased sensitization of the central nervous system. It is thought that such sensitization serves as a possible neuronal substrate for amplification of normal bodily sensations so that these perceptions lead to distress, complaints, and somatic symptoms, along with impairments in social, occupational, and health functioning.^{6–8}

INFLAMMATORY CYTOKINES

Inflammatory cytokines are potent, low-molecular-weight proteins and glycoproteins that are secreted by white blood cells and assist in the development and proliferation

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Psychiatr Clin N Am 34 (2011) 605–620

doi:10.1016/j.psc.2011.05.005

0193-953X/11/\$ – see front matter © 2011 Elsevier Inc. All rights reserved.

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of immune cell subsets, and in the promotion of nonspecific innate as well as adaptive immune responses. Examples of inflammatory cytokines are interleukin (IL)-1 β , IL-2, IL-6, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ , which together promote a variety of cell functions that stimulate and lead to an inflammatory cascade in response to infection or tissue injury. Although there are non-immune cells that can produce and express certain inflammatory cytokines (eg, adipocytes release IL-6), immune cells are the primary source of these cytokines. When released by tissue resident macrophages, inflammatory cytokines increase vascular permeability and cellular adhesion, allowing cells to leave the blood vessels and migrate to the site of infection. In turn, immune cell expression of endothelial adhesion molecules is induced, which promotes firm adhesion of the immune cell to endothelial cells so that these cells can migrate from the circulation to tissue. The migration of cells is further directed by inflammatory cytokines, which activate the expression of chemokines that assist in the adhesion process and guide cells to their proper destinations in tissues via chemical diffusion gradients. Finally, certain proinflammatory cytokines, including IL-6 and TNF- α , promote liver production and release of acute phase proteins such C-reactive protein (CRP), which acts a mediator of systemic inflammation. Together, these inflammatory cytokines and acute phase proteins induce additional systemic effects, including regulation of metabolic responses to pathogens with coordination of fever, for example, with additional effects on physiology as well as behavior. Hence, in this capacity, inflammatory cytokines function in a manner similar to neurotransmitters and hormones in mediating specific physiologic responses, which rely on receptor–ligand interactions with self (autocrine), local (paracrine), and distal (endocrine) effects.

COMMUNICATION PATHWAYS BETWEEN INFLAMMATORY CYTOKINES AND THE BRAIN

Inflammatory cytokines communicate with the brain through cellular, molecular, and/or neural mechanisms. Because cytokines are large proteins, they do not efficiently cross the blood–brain barrier via passive transport.⁹ Nevertheless, in areas where the blood–brain barrier is not present (eg, circumventricular sites), circulating concentrations of cytokines can enter the central nervous system, and in so doing stimulate the release of central cytokines via activation of inflammatory mediators such as prostaglandins of the E2 series from macrophage-like cells that exist in the circumventricular organs.^{2,10} Additionally, the cytokines that are produced in the circumventricular organs gradually diffuse into the brain side of the blood–brain barrier and recruit microglial cells in the brain parenchyma to form a cellular and molecular representation of the peripheral immune response. Second, peripheral cytokines can also communicate with the brain by binding to cerebral vascular endothelium. Again, binding of cytokines at receptor-dependent sites facilitates the release of active second messengers such as nitric oxide, which induces central cytokine activation. Third, cytokines can be actively transported across the blood–brain barrier via carrier-mediated mechanisms. Together, these communication pathways involving either macrophage-like cells residing in circumventricular organs, second-messenger activation, or active transport provide 3 overlapping cellular and molecular mechanisms by which the brain actively senses circulating cytokines and monitors changes in the composition of the internal milieu.⁹

Neural mechanisms also play a critical role in communication of the immune system with the brain. Afferent nerves innervate bodily sites, and at sites of inflammation, these afferent nerves become activated to promote the perception of the sensory components of inflammation (*calor* or heat and *dolor* or pain). Additionally,

such activation of afferent nerves induces the expression of brain proinflammatory cytokines in response to peripheral inflammatory cytokines.⁶ Indeed, a number of experimental findings support the role of afferent nerves in the immune-to-brain communication; bilateral section of the vagus nerve blocks inflammatory signaling from the abdominal cavity,^{11,12} and a section of the trigeminal nerves does the same for oral inflammation.¹³ Additionally, inflammatory signaling of afferent nerves such as the vagus occurs by receptor dependent binding of IL-1 β , for example, on paraganglia that surround the terminals of the vagus. Moreover, circulating IL-1 β is reported to stimulate vagal sensory activity,¹⁴ which induces acetylcholine release from paraganglia neurons. Subsequently, activation of afferent vagal fibers sends neural impulses and signals the dorsal motor nucleus via the nucleus tractus solitarius, resulting in the production and release of proinflammatory cytokines in the brain.^{6,15}

Counterregulatory neural mechanisms have also been defined that dampen peripheral inflammation, once central activation of inflammatory signaling occurs. Again, the vagus plays a critical role; activation of the efferent vagal pathway inhibits inflammation in the periphery at paraganglia sites via cholinergic mechanisms.¹⁶ In summary, this neural pathway, or “inflammatory reflex,” is a relatively fast-acting mechanism compared with the cellular pathways described.

INFLAMMATORY CYTOKINES AND SICKNESS BEHAVIOR: EVIDENCE FROM BASIC STUDIES

Studies in laboratory animals provide compelling evidence that administration of innate immune cytokines can induce a syndrome of “sickness behavior” that has many overlapping features with the somatic behavioral comorbidities commonly experienced by patients with somatoform disorder, including hyperalgesia, impaired sleep, and fatigue.^{17,18} These effects of cytokines seem to be secondary to the capacity of peripheral cytokine signals to access the brain and activate inflammatory responses within the brain, which then interact with pathophysiologic pathways known to be involved in behavioral disorders.¹

In response to peripheral inflammatory signaling, certain classes of brain cells, including microglial cells and astrocytes secrete cytokines.¹⁹ Such endogenous expression of cytokines, and associated cytokine receptors, have been found throughout the brain, including the hypothalamus, basal ganglia, cerebellum, circumventricular sites, and brainstem nuclei.²⁰ Additionally, multiple cytokines are expressed in the brain, including each of the prominently described inflammatory cytokines such as IL-1 β , TNF- α , IL-6, and IFN- γ . Each of these cytokines have been found to promote the release of neurotransmitters, including norepinephrine, dopamine, and serotonin,^{19,20} implicating central inflammatory cytokines in the initiation or modulation of neurochemical cascades that directly affect behavior.

Inflammatory cytokines, via their interaction with central nervous system mechanisms, induce a constellation of behavioral responses, which was first described in animals as sickness behavior as a result of infection.²¹ Sickness behavior includes disturbance in sleep–wake activity with alterations in measures of sleep continuity and architecture, decreases in daytime activity, as well as decreased interest in feeding, grooming, and socializing. Although the adaptive significance of these behaviors is not known, it is thought that these sickness behaviors allow the “sick” animals to more efficiently mobilize immune defenses against an unwanted pathogen.²² Several lines of evidence support the role of inflammatory cytokines in driving these behavioral responses. Central or peripheral stimulation with cytokines (IL-1 β or TNF- α) or endotoxin [lipopolysaccharide (LPS)] leads to decreased activity, hypersomnia, decreased feeding behavior, learning impairment, and social withdrawal.^{23,24}

Conversely, antagonism of central cytokine activity via immunoneutralization or receptor-mediated blockade (eg, administration of IL-1 receptor antagonist) blocks the behavioral effects of peripheral immune activation. Further studies have found that the vagus nerve transduces the peripheral inflammatory signal to the brain; vagotomy has been found to attenuate sickness behavior responses but not to alter plasma levels or cytokine production by peritoneal macrophages.^{11,25} Importantly, the vagal pathway seems to impact behavioral, but not necessarily febrile, response to inflammation.²⁶

Coupled with regulation of behavioral responses to inflammatory challenge, inflammatory cytokines induce associated alterations in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis. For example, first described as “endogenous pyrogen,” IL-1 β has been found to increase HPA axis function via the activation of corticotrophin-releasing factor in the paraventricular nucleus of the hypothalamus.²⁷ In turn, such HPA activation is thought to have counterregulatory effects and to dampen and control the inflammatory response, thus, defining a negative feedback loop.

INFLAMMATORY SIGNALING: THE ROLE OF STRESS

The physiologic linkages between inflammation and HPA axis activation suggest the possibility that stress, which is well known to have effects on HPA axis activation, might have a role in the pathophysiology of the immune-to-brain communication. Indeed, there seems to be a cross-sensitization between stressors and cytokines. Exposure to stress, for instance, sensitizes the peripheral as well as central cytokine responses. For example, after administration of a stressor such as inescapable electric shock, an immune challenge such as a dose of bacterial LPS is associated with an augmented inflammatory response as compared with a response in animals not previously exposed to stress.²⁸ Reciprocally, after IL-1 has been previously given, subsequent administration of inescapable electric shock induces an exaggerated HPA response for up to 2 to 3 weeks after the cytokine was given.²⁹ Additionally, sensitization can also occur when the same cytokine is administered twice at an interval of several days or weeks, and it affects both cytokine-sensitive neurotransmitter metabolism and pituitary–adrenal responsiveness to cytokines.³⁰

Further data show that stressful stimuli have independent effects on inflammatory biology dynamics. Acute stressors activate inflammatory cytokines and their signaling pathways [eg, nuclear factor kappa B (NF- κ B)] both in the periphery and in the brain.^{31,32} In addition, data from rats indicate that stress can activate microglia in the brain and increase their sensitivity to immunologic stimuli such as LPS. Such activation of IL-1 in the brain reduces the expression of brain-derived neurotrophic factor (BDNF), which may have further effects on behavior; BDNF is believed to play a pivotal role in neuronal growth and development, learning, synaptic plasticity, and ultimately behavioral disorders.³³

Activation of the sympathetic nervous system and the release of catecholamines that bind to α - and β -adrenergic receptors on relevant cells are thought to mediate the effects of stress on brain inflammatory pathways.^{32,34} Conversely, activation of the parasympathetic nervous system via the release of acetylcholine seems to inhibit inflammatory signaling pathways (eg, NF- κ B),³⁵ suggesting that sympathetic and parasympathetic pathways have opposing influences on inflammatory responses during stress.

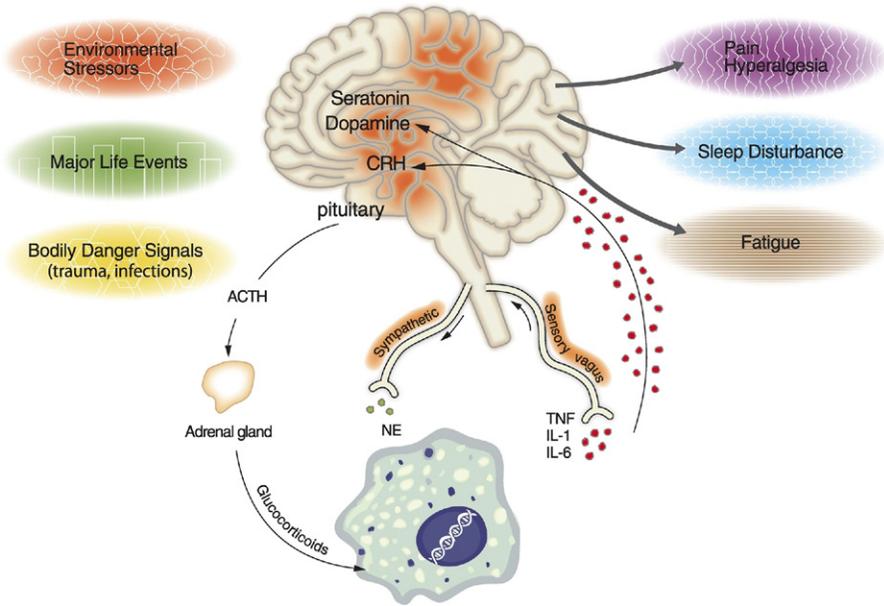


Fig. 1. Associations between environmental stress, life events, and trauma, activation of peripheral inflammation, and increases in central inflammatory signaling, which together are thought to contribute the occurrence of somatic symptoms of pain or hyperalgesia, sleep disturbance, and fatigue.

INFLAMMATION AND BEHAVIORAL SYMPTOMS IN HUMANS: GENERAL CONSIDERATIONS

Advances put forth from animal studies contrast with our limited understanding of the mechanistic role of inflammatory cytokine activity on sickness behavior-related symptoms (eg, hyperalgesia, sleep disturbance, and fatigue) in humans. Most of the evidence linking inflammatory immune activation and sickness behavior in humans is generated from naturalistic observations, which correlate elevated levels of cytokines with behavioral alterations. Nevertheless, there are also some experimental data showing that acute activation of proinflammatory cytokine activity and/or the acute and chronic administration of cytokines has a number of behavioral effects. Among the behavioral disturbances induced by cytokines, the induction of depressive symptoms is probably the most studied. Indeed, the administration of IFN- α , a potent inducer of inflammatory activity, leads to hallmark symptoms of depression, such as anhedonia and feelings of sadness, along with a range of other neurobehavioral changes, including disturbed sleep, fatigue, and loss of appetite.^{36,37} Because these symptoms fully remit after cessation of cytokine therapy, it is thought that such inflammatory activity drives the onset of these symptoms.²⁰ Further, administration of immune challenges that provoke the activation of inflammatory responses leads to increases in feelings of fatigue and depressed mood.^{38,39} Inflammation-driven changes in mood seem to be associated with neural changes such as reduced functional connectivity between the subgenual anterior cingulate cortex, amygdala, and medial prefrontal cortex,⁴⁰ as well as reduced ventral striatum activity in response to reward cues (**Fig. 1**).^{38,39}

INFLAMMATION AND PAIN: TRANSLATION OF BASIC RESEARCH TO HUMANS

Pain is among the most prominent of the somatization symptoms, and such pain is characterized as pain for which there is no definable etiology in the body. Alternately, such pain is perceived as exaggerated, resulting from identifiable peripheral causes but in which sensations from the affected body region are grossly abnormal. For example, environmental stimuli that would not be normally perceived as painful are now perceived as such, whereas environmental stimuli that would typically be perceived as painful now evoke an amplified and/or persistent perception of pain.⁴¹ Furthermore, in addition to perceptions of pain, simple environmental stimuli may evoke abnormal feelings of electric tingling or sensations that have other unusual and unpleasant qualities. This spontaneous pain, evoked by environmental stimuli or not, can occur frequently, at varying qualities, and throughout the body in varying locations. Increasingly, the immune system is thought to have a role in such pathologic pain states⁴¹ and possibly in the occurrence of neuropathic pain found in somatization disorders, as well as in disorders that have an inflammatory basis.

Immune cells in and around peripheral nerves, and immune-like glial cells in spinal cord, are key players in both the creation and maintenance of pathologic pain states. Basic research has found that these immune cells, including macrophages, produce proinflammatory cytokines (eg, TNF- α , IL-1 β , IL-6) after trauma; such increases of these cytokines parallel increases in pain perception.^{42,43} Indeed, the magnitude of neuropathic pain correlates with both the number of activated macrophages and the number of IL-6-producing cells at the site of injury.⁴²

Other experimental data from animals indicate a role of proinflammatory cytokines in the endogenous mediation of neuropathic pain. For example, experimental injection of proinflammatory cytokines onto or into peripheral nerves enhances pain responsiveness.^{44,45} In contrast, blockade of proinflammatory cytokine actions at the level of the sciatic nerve reduces neuropathic pain, as well as reducing immune cell recruitment and demyelination.⁴⁶ Likewise, neuropathic pain can be abrogated by treatments that decrease proinflammatory cytokines and/or increase anti-inflammatory cytokines such as IL-10.⁴⁷ Finally, in animals that lack the IL-6 gene (ie, IL-6 knockout mice), neuropathic pain does not seem to occur.⁴⁸

Neuropathic pain or hyperalgesia often overlaps with other sickness behaviors, possibly owing to common underlying inflammatory biology. For example, immune activation in the periphery elicits hyperalgesia along with other sickness behaviors.⁴¹ Similarly, administration of an immune challenge (eg, bacterial endotoxin) or doses of inflammatory cytokines signals pain responses,⁶ in concert with provoking sickness behaviors.⁶ In turn, pharmacologic blockade of TNF- α , for example, prevents sickness-induced hyperalgesia as well as other sickness behaviors. Importantly, central mechanisms mediate the action of proinflammatory cytokines on hyperalgesia. For example, peripheral administration of IL-1 β elicits thermal hyperalgesia owing to the de novo production and release IL-1 β within the brain, which can be antagonized by central administration of an endogenous antagonist of IL-1 β (α -melanocyte-stimulating hormone).⁴⁹ Additionally, there is synergistic overlap between proinflammatory cytokines; TNF- α creates hyperalgesia by inducing the release of brain IL-1 β ,⁵⁰ and all 3 proinflammatory cytokines (TNF- α , IL-1 β , IL-6) produce hyperalgesia via the release of prostaglandins,⁵¹ substances repeatedly implicated in exaggerated pain states.

Translation of these basic studies to humans is limited, but this is clearly an issue that warrants serious consideration, given the prominent links between pain and inflammatory disorders, as well as chronic conditions such as metabolic disorder and

obesity. Indeed, emerging data in humans support the notion that inflammation may contribute to hyperalgesia and neuropathic pain in cases where no known etiology can be readily identified. For example, among person with AIDS, more than 80% of these patients suffer from chronic pain, and of these, most suffer from vague and diffuse pains of unknown origin.^{52,53} Although patients with AIDS suffer from pain from a variety of readily identifiable causes, including nerve damage, opportunistic cancers, and opportunistic infections from the disease as well as the drugs used in therapy, there is evidence that HIV-1 activation of spinal cord glia may in itself drive and/or perpetuate pain in these patients, creating pain for which there is no definable etiology in the body, as well as exaggerating pain resulting from identifiable peripheral causes. Indeed, the perception of pain is strongly amplified under the effect of proinflammatory mediators produced by activated glial cells in the spinal cord.⁵⁴ Additionally, glial activation is not restricted to the spinal cord, but also occurs in the brain in chronic inflammation associated, for instance, with progressive neurodegeneration,⁵⁵ obesity,⁵⁶ or aging. Together, it is hypothesized that the brain cytokine system becomes sensitized and responds to a greater extent to further activation of the peripheral innate immune system, which results in a more intense cytokine-induced sickness behavior (somatic amplification) and/or a delayed recovery from sickness.

INFLAMMATION AND SLEEP DISTURBANCE

Sleep complaints and associated daytime fatigue are thought to affect 30% to 40% of the general US population,⁵⁷ with 10% meeting criteria for chronic syndromal insomnia.⁵⁸ The prevalence of sleep complaints and syndromal insomnia is even higher among patients with medical disorders, and this is especially the case for those who suffer from chronic conditions with pain and/or underlying inflammation such as rheumatoid arthritis. Activation of inflammatory signaling can occur in the midst of sleep disturbance, and increases in inflammation have reciprocal effects on sleep, which together is thought to lead to a vicious cycle of sleep disturbance and inflammation, which perpetuates over time contributing to fatigue, and possibly depression. Hence, sleep disturbance might be viewed as principal behavioral culprit in the association between inflammation and multiple somatic symptoms.

Acute and chronic sleep disturbances are associated with immune alterations. Initial studies demonstrated that sleep loss results in decreases in innate immunity as reflected by decreases in the activity of natural killer cells.^{59,60} However, sleep loss can also have activating effects on certain aspects of the immune system, leading to increases in inflammatory markers such as IL-6, TNF- α , and CRP.^{61,62} Furthermore, studies reveal that systemic increases in markers of inflammation are due to increased activation of cellular and genomic inflammatory mechanisms.⁶³ Partial night sleep deprivation, which is thought to mimic the kind of sleep loss often found in persons undergoing stress and/or suffering from a chronic medical disorder, is associated with increased monocyte production of IL-6 and TNF- α , as well as a greater than 3-fold increase in IL-6 messenger RNA and a 2-fold increase in TNF- α messenger RNA.⁶³ Monocytes are the primary immune cell source of proinflammatory cytokines. Interestingly, females show an exaggerated production of these cytokines after sleep loss,⁶⁴ which may be due to a greater activation of NF- κ B in females as compared with males.⁶⁵ NF- κ B is a transcription factor that has a critical role in initiating the inflammatory cascade, which leads to the production of cellular proinflammatory cytokines. An exaggerated activation of inflammatory signaling in females after sleep disruption has broad implications for understanding the increased risk of associated behavioral symptoms such as fatigue and depression in females, as

well as a nearly 2-fold increase in the prevalence of disorders with an inflammatory basis (autoimmune disorders) in females compared with males.

Given these experimental data, it is not surprising that chronic sleep disturbance and clinical insomnia are associated with increases in inflammation as indexed by elevated levels of IL-6 and TNF- α .⁶⁶ In turn, such daytime elevations of proinflammatory cytokine seem to drive symptoms of fatigue; antagonism of TNF- α by pharmacologic blockade produces a partial improvement in symptoms of sleepiness, for example.⁶⁷

The role of cytokines in the regulation of sleepiness raises the possibility that proinflammatory cytokines might also alter sleep during the night. Indeed, substantial evidence from animal studies reveal that IL-1 β , TNF- α , and IL-6 all have a role in the homeostatic regulation of sleep.⁶⁸ For example, the central injection of IL-1 β increases non-rapid eye movement (NREM) sleep time and suppresses rapid eye movement (REM) sleep.⁶⁹ Similarly, in animal models of infection, there are striking changes in sleep that parallel the alterations found after doses of proinflammatory cytokines, including increases in NREM sleep during times of usually high activity.⁷⁰ Interestingly, differences in sleep response to infection are partly attributed to genetic variants that contribute to differential increases in proinflammatory cytokines. In animals with genetic alleles that produce high levels of type 1 IFN- α and IFN- β , there are greater amounts of NREM sleep compared with animals with alleles associated with decreased production of these IFNs.⁷¹ Such genetic variability has implications for understanding differences in the risk of sleep disturbance among populations who are exposed to inflammatory challenge.

In humans, studies that evaluate the effects of cytokines on the regulation of sleep are limited. Administration of endotoxin (*Salmonella abortus*, a LPS that stimulates proinflammatory cytokine production by macrophages) has been found to increase NREM stage 2 sleep, whereas slow-wave sleep and stages 3 and 4 are relatively unaffected.^{72,73} In contrast, subcutaneous injection of IL-6 as well as IFN- α induce a reduction of slow-wave sleep, as well as REM sleep.^{74,75} Finally, chronic IFN- α administration in patients with hepatitis C, who had no prior sleep disorder was associated with increases in wake after sleep onset, as well as decreases in slow-wave sleep and sleep efficiency.⁷⁶ Finally, Irwin and colleagues⁷⁷ demonstrated in a randomized, placebo-controlled study that neutralization of TNF- α activity was associated with a significant reduction of REM sleep in abstinent alcohol dependent patients, who have elevated amounts of REM sleep. Moreover, individual biologic variability in the degree of TNF antagonism, as reflected by circulating levels of soluble TNF receptor type II, correlated with declines in REM sleep.⁷⁷ Taken together, these data further support the hypothesis that circulating levels of TNF- α , as well as possibly other proinflammatory cytokines, may have a physiologic role in the regulation of NREM and REM sleep amounts in humans.

On a behavioral level, dysregulation in sleep may trigger fatigue,⁷⁸ and in turn chronic fatigue itself triggers sleep disturbance, possibly through alterations in sleep-wake activity chronobiology. Indeed, the co-occurrence of fatigue and sleep disorders is common, making it difficult to determine the causal symptom. Specific precipitating as well as perpetuating factors for sleep disturbance, and for fatigue, relate also to the presence and nature of a particular comorbid disorder, as well as the social and behavioral contexts and responses to initial dysregulation.

INFLAMMATION AND FATIGUE

Fatigue, which may be mostly viewed as “tiredness” or “lack of energy,” has many components that might underlie its onset and persistence, including physiologic (eg,

pain and anemia), psychological (eg, changes in mood), social/interpersonal, and chronobiological (eg, circadian rhythms disorders and sleep disruption) factors.⁷⁹ Peripherally related fatigue (fatigue associated with an inability for the musculature to transmit central nervous system signals) is the kind that is experienced more on a somatic level, whereas centrally related fatigue (which results in an inability to engage in or maintain voluntary activities) is the kind that includes the cognitive, motor, emotional, and social aspects of fatigue.⁸⁰ Fatigue is a common symptom of many other medical conditions and hence is a common somatic symptom found across disorders.

Basic research in animals has found that fatigue, as indexed by activity, can be elicited along with other sickness behaviors in association with immune activation, similar to findings with pain and sleep. In humans, the links between inflammation and fatigue are found across multiple medical comorbidities, with increases in inflammation correlating with fatigue among individuals with multiple sclerosis,⁸¹ Sjögren syndrome,⁸² and rheumatoid arthritis,⁸³ among others. Furthermore, among healthy persons, longitudinal studies have shown that plasma levels of the proinflammatory marker CRP predict the development of fatigue.⁸⁴ However, the most compelling evidence for an association between inflammation and fatigue has been most thoroughly generated in cancer populations. For example, a qualitative review examined the association between proinflammatory cytokines and fatigue in cancer patients before, during, and after treatment, and generally supported a finding of a positive association between inflammation and fatigue.⁸⁵ The reasons for such a prominent link between inflammation and fatigue in cancer populations is not fully understood, although tumors can secrete inflammatory cytokines and cancer treatments (radiation, chemotherapy) can induce inflammation. Indeed, chemotherapy-related alterations in proinflammatory cytokines, with reported increases in IL-6, IL-10, and serum soluble receptor 1 for TNF correlate with increases in symptom severity among non-small cell lung cancer patients⁸⁶ as well as breast cancer patients,⁸⁷ and these effects can be partially abrogated by the pharmacologic blockade of TNF- α .⁸⁸ Similar associations between inflammation and fatigue have also been found during radiation therapy in cancer patients, including in breast and prostate cancer patients undergoing radiation therapy.⁸⁹

Similar to the sensitizing effects of cytokine on pain responses, it is possible that treatment-induced elevations in inflammatory markers sensitize peripheral and central mechanisms, which contribute to an amplification and/or perpetuation of inflammation and effects on fatigue symptoms. For example, even after chemotherapy and/or radiation treatments are over, fatigue lingers in about one third of survivors, with symptoms persisting for up to 10 years.⁹⁰ Those persons with persistent posttreatment fatigue have increased levels of a number of proinflammatory markers including plasma levels of IL-6, its soluble receptor, IL-1 receptor antagonist, CRP, soluble TNF receptor type II, and neopterin.^{91,92} Additional studies suggest that underlying cellular and genomic activation of inflammatory biology dynamics drive these effects with increases in the cellular production of IL-6 and TNF- α found in fatigued versus-fatigued breast cancer survivors⁹² and with an upregulation of the proinflammatory transcription factor NF- κ B.⁹³ Again, genetic variants that contribute to variability in the expression of inflammation seem to be associated with differential risk of somatic symptoms, including fatigue; polymorphisms in inflammation-related genes are associated with increased risk of cancer-related fatigue.⁹⁴ Together, these data raise important questions about the development of treatments that specifically target inflammation for the treatment of fatigue, although such studies remain in development.

Treatment with TNF antagonists has, however, been associated with reductions in fatigue among individuals with inflammatory conditions such as psoriasis.⁹⁵

Treatment Implications

The number of potential integrated mechanisms by which inflammatory cytokines might drive the onset of somatic symptoms, including the role of stress response pathways in initiating and perpetuating this cycle, suggests the opportunity for multiple targets and/or for efficacy of various treatments. To this end, there is limited evidence from randomized, controlled trials that both pharmacologic (anti-depressants) and nonpharmacologic (aerobic exercise, cognitive-behavioral therapy) treatments are able to attenuate some somatic symptoms such as sleep disturbance and fatigue, with possible attendant effects on inflammation. Little is known about whether inflammation mediates these outcomes, and treatments that specifically target activation of the brain cytokine system are not yet available.

Cognitive-behavioral, supportive, or insight-oriented treatments that target stress mechanisms may be especially relevant, given the potential role of stress-induced inflammation and altered regulation of inflammatory responses by the neuroendocrine system. Such behavioral strategies broadly vary, but are designed to reduce symptom severity. These approaches include relaxation training, enhancement of coping skills, graded exercise, and cognitive-behavioral therapy. Indeed, both cognitive-behavioral stress management and mindfulness-based stress reduction have been shown to alleviate psychological distress in certain patient populations (eg, breast cancer patients), while increasing lymphocyte proliferative responses and normalizing diurnal cortisol secretion.^{96,97} There is also evidence that aerobic exercise can lead to reductions in inflammatory markers,⁹⁸ and that interventions that target both the mind and body (eg, a movement meditation, Tai chi) can mitigate age-related increases in inflammation among older adults.⁹⁹ Interestingly, recent studies using cognitive-behavioral therapy program, on the one hand, and Tai Chi on the other, found improvements in health functioning and physical activity, along with improvements in sleep and fatigue as compared with an active educational control condition.¹⁰⁰ However, the role of inflammatory mediators in driving these benefits has not been systematically investigated. For example, exercise interventions, which have shown beneficial effects on both fatigue and inflammatory markers,⁹⁸ have not evaluated whether decreases in inflammation mediate changes in fatigue outcomes. Likewise, a randomized, controlled trial of QiGong demonstrated decreases of fatigue and inflammation (as indexed by serum CRP levels),¹⁰¹ but the mediating role of CRP was not assessed.

It is hypothesized that blockade of most upstream elements in the cytokine-central nervous system-behavior cascade may ameliorate complaints of pain, sleep disturbance, and fatigue; hence, it is also logical to consider biological treatments such as cytokine antagonists, anti-inflammatory agents, and drugs that disrupt cytokine signaling pathways (eg, NF- κ B and p38 MAPK). Several trials have demonstrated that TNF- α blockade with etanercept can improve cancer-related fatigue, and other studies have found that administration of etanercept or another biological agent that block TNF- α [infliximab (Remicade)] can lessen daytime sleepiness and partially normalize sleep in rheumatoid arthritis patients, as well as those with alcohol dependence.^{88,102,103}

Given evidence that inflammation can alter certain central nervous system neurotransmitters, including monoamines and serotonin pathways, pharmacologic agents that target these specific systems may benefit related symptom domains (eg, dopamine-active drugs for fatigue and psychomotor slowing). For example, dopaminergic agents

such as methylphenidate (a psychostimulant) have been shown to treat fatigue in patients undergoing cancer treatments.¹⁰⁴

Finally, drugs that enhance glucocorticoid-mediated negative feedback, through facilitation of glucocorticoid receptor function, may control corticotropin-releasing hormone overexpression and have additional action to inhibit inflammatory pathways.¹⁰⁵ Novel treatments supporting neuronal integrity/plasticity (neuroprotective agents), including drugs that stimulate the activity or signaling of relevant growth factors (eg, BDNF), may be especially important for future development, given the links of BDNF with pain responsiveness.

SUMMARY

Many somatization symptoms, including pain, sleep disturbance, and fatigue, may represent activation of the central nervous system cytokine system in response to peripheral inflammatory signaling after stress, infectious challenge, or noninfectious trauma. Some clinical data show that activation of inflammatory signaling along with increases in the peripheral expression of proinflammatory cytokines correlates with, and possibly drives, the onset and persistence of these somatic symptoms. However, most data have been accumulated in healthy or chronic disease populations; there are limited findings linking these inflammation and symptoms of somatic distress in patients with somatoform disorders. One study found that patients with somatization, as well as those with major depression, had increases in circulating levels of IL-1 receptor antagonist as compared with healthy controls.¹⁰⁶ There are no other data, to our knowledge, that have systematically examined the associations between inflammation and somatic symptoms in patients with somatoform disorder. Moreover, no study has examined whether blockade of proinflammatory cytokine activity might improve symptoms of pain, sleep disturbance, and fatigue among patients with somatoform disorder.

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