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Human psychoneuroimmunology: 20 Years of discovery

Michael R. Irwin *

Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience, University of California, 300 Medical Plaza, Suite 3-109, Los Angeles, CA 90095-7057, USA

Abstract

An important component of psychoneuroimmunology research is to reveal the myriad ways that behaviors and health are inter-related, with a focus on the immunological mechanisms that underlie these interactions. Research in human psychoneuroimmunology has shown that immunoregulatory processes are an integral part of a complex network of adaptive responses. As such, this review provides a perspective from our laboratory over the last 20 years to define the inter-relationships between behavior and immunity; to identify the hypothalamic pituitary adrenal (HPA) and autonomic mechanisms that link the central nervous system and immune responses; to examine the clinical implications of immune alterations during depression or life stress on inflammatory and infectious disease risk; and to explore the reciprocal role of immune mediators on behavior in humans.
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1. Introduction

Increasing public health attention has focused on the contribution of psychosocial factors, behaviors, and behavioral disorders to chronic disease and health. In two separate reports from the Institute of Medicine, *Health and Behavior* (IOM, 1982) and *Health and Behavior* (IOM, 2001), research efforts aimed at understanding the interplay among biological, behavioral, and social factors in health and disease have been identified and integrated. This broad examination of mind–body interactions and health has shown many reciprocal links among the central nervous system, which recognizes and records experiences; the autonomic and neuroendocrine system, which produces neurotransmitters and hormones that govern many bodily functions; and the immune system, which organizes responses to infections and other challenges. Research in the field of psychoneuroimmunology provides an integra-

tive frame across these physiological mechanisms, and brings together the study of these systems to reveal the myriad ways that behaviors and health are inter-related, with a focus on the immunological mechanisms that underlie these interactions. As such, this review provides a 20 years overview from our laboratory to define the inter-relationships between behavior and immunity; to identify the hypothalamic pituitary adrenal (HPA) and autonomic mechanisms that link the central nervous system and immune responses; to examine the clinical implications of immune alterations during depression or life stress on inflammatory and infectious disease risk; and to explore the reciprocal role of immune mediators on behavior in humans.

2. Documenting immune alterations

The nascent field of human psychoneuroimmunology emerged as interdisciplinary effort to understand the links between brain, behavior, and the immune system, as epidemiologic evidence demonstrate the influence of psychological

* Fax: +1 310 794 9247.
  E-mail address: mirwin1@ucla.edu

stress and depression on morbidity and mortality risks. Early studies in animals had found that stress was associated with increased susceptibility to infectious disease (Rasmussen et al., 1957), as well as inflammatory disease (e.g., adjuvant-induced arthritis) (Amkraut et al., 1971). Hence, there was speculation that changes in the immune system might be a relevant mechanism linking between stress and morbidity in humans. Indeed, one of the most severe psychological stressors, conjugal bereavement, was found to be associated with robust declines in cellular immune responses by the assessment of mitogen induced lymphocyte proliferation (Bartrop et al., 1977; Schleifer et al., 1983). However, the clinical implications of these immune alterations were not known.

Natural killer (NK) cells were increasingly viewed as important immune components in the first line of defense against viral infections; NK cells were also thought to have a role in tumor surveillance. Biron et al. had described the presence of severe herpes virus infections in a person without NK cell function (Biron et al., 1989), whereas Rosenberg et al. had discovered that the induction of lymphokine activated killer cells by high dose interleukin (IL)-2 treatment led to a regression of metastatic disease in patients with advanced cancer, although such treatments were associated with considerable toxicity (Rosenberg et al., 1987). Moreover, Shavit and colleagues had found that brain release of opiate peptides mediated stress-induced suppression of NK activity in animals (Shavit et al., 1984).

Given these emerging data on the clinical relevance of NK cells and findings that NK cells could be modulated by neural processes, it was hypothesized that severe psychological stress following the death of a spouse might lead to decreases of NK activity. Initial findings confirmed this notion, and as extensively reviewed by Irwin and Miller (2007), decreases of NK activity and other cellular immune responses were found in persons undergoing severe life stress. Further evidence demonstrated found that the severity of psychological response to such stressors, as indexed by depressive symptoms, was a key correlate of declines of NK activity (Irwin et al., 1987a). A similar reduction of NK activity was found in patients with major depression, which resolved once the depressive episode had remitted (Irwin et al., 1990a,c, 1992b; Irwin and Miller, 2007).

The link between depression and cancer has been long debated (Irwin and Miller, 2007), with variations in levels of NK activity being implicated as one possible factor. Familial differences in NK activity, for example, are associated with differences in familial risk of cancer (Bovbjerg and Vladimardsdottir, 1993). Further psychoneuroimmunology studies sought to examine this question, by exploring whether additional behavioral factors that might act in concert with depression to contribute to immune alterations relevant to cancer risk. In a large epidemiologic study, Linkins and Comstock found that depression predicted cancer mortality, but that this association was found only in persons who were tobacco smokers (Linkins and Comstock, 1990). Yet, in over two dozen studies of depression and immunity, the contribution of smoking histories to immune alterations was typically neglected despite the high prevalence of smoking in depressed patient populations. Among 245 depressed patients and comparison controls stratified by smoking status, we found that depression and smoking status interact to produce greater declines of NK activity than changes found in depressed or smoking groups alone (Jung and Irwin, 1999). Further studies extended this line of inquiry and demonstrated that co-morbidity of depression and alcohol dependence also leads to greater declines of immunity than either depression or alcohol dependence alone (Irwin et al., 1990a,c). Similarly, recent work has found that cocaine dependence is associated with a striking reduction of Toll-4 (TLR-4) stimulated production of inflammatory cytokines, which may explain the increased risk of these patients for infectious disease including HIV-related secondary bacterial infections (Irwin et al., 2007a).

In summary, these data were among the first to show that behavioral states could influence immunity in humans; replication of these findings provided a firm foundation for further studies that probed the effector pathways by which the brain can influence immunity (see Fig. 1). Moreover, these immunological findings yielded novel insights into a potential pathway by which stress could impact health and possibly contribute to morbidity risk in depression and stress.

3. CRH: a central neuropeptide model of stress

Psychological stress serves as an excellent clinical model to learn more about the interactions between the brain and immune system, as stressed patients exhibit prominent abnormalities of behavior (e.g., depressed mood, impaired sleep), along with dysregulation of the neuroendocrine- and sympathetic nervous systems (SNS), which were hypothesized to be key efferent pathways in the regulation of immunity by the brain (Fig. 1). However, as noted above, these initial studies were primarily clinical, observational in design, and the salient mechanisms were not explored. Brain processes might be one of the mediating factors since it is known that health behavior is one of the strongest mediators of the relationship between stress and disease.

To understand how the brain modulates immunity, a rat animal model was developed that focused on central corticotropin releasing hormone (CRH) (Irwin et al., 1987b). Depressed patients show elevated levels of CRH in the central nervous system as measured by radioimmunoassay of cerebrospinal fluid, and this key central neuropeptide is involved in integrating behavioral, neural, neuroendocrine, as well as immune responses to stress. A series of studies demonstrated that acute central doses of CRH induce robust declines in innate and cellular immune responses (Irwin et al., 1987a,b,1989; Strausbaugh and Irwin, 1992), and showed for the first time that this peptide acted within
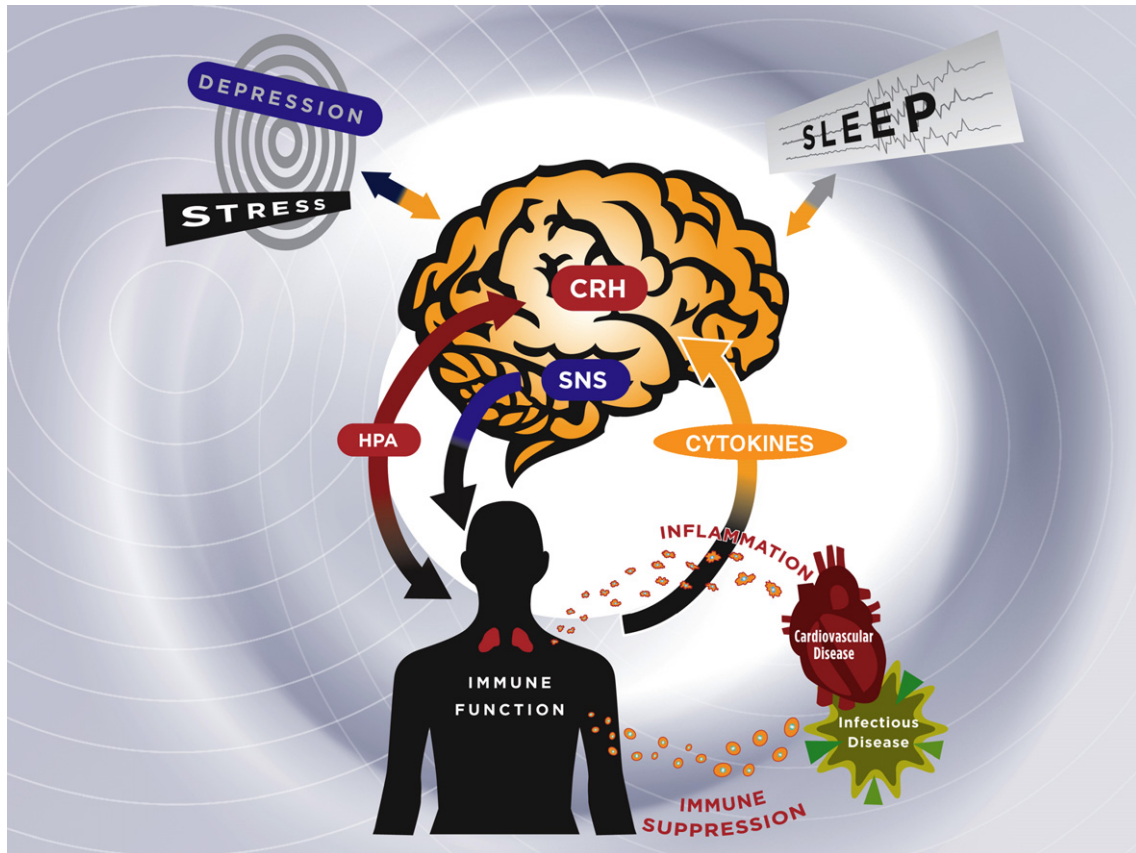
Fig. 1. Research themes in human psychoneuroimmunology.

the brain to could coordinate changes in peripheral immunity as indexed by ex vivo assays.

Additional studies sought to provide an assessment of the effects of CRH on an integrated in vivo action of the immune system, namely, an antibody response to a novel antigen (Irwin, 1993a). Following immunization with a soluble T-cell-dependent protein antigen and measurement of the kinetics and magnitude of the specific antibody response, central doses of CRH at the time of immunization were found to induce robust declines in the magnitude of IgM and IgG specific antibody responses. IL-1 induces the central release of CRH, and central doses of IL-1 were also found to induce a similar suppression of antibody responses. Together, these data suggest that under conditions in which CRH is released, such as stress or possibly depression in humans, the in vivo immune response may be downregulated, leading to a delay in the synthesis of adequate levels of antibodies and failure of the immunological protection of the host to an infectious agent. These findings were also relevant for understanding immune dysregulation in aging, as responses of sympathetic activation and immune suppression are exaggerated following administration of CRH in old rats as compared to young animals (Irwin et al., 1992a).

By using specific CRH receptor antagonists that were administered centrally vs. peripherally, CRH was found to act in the brain via receptor dependent mechanisms to induce acute changes in immune responses (Irwin et al., 1989). Furthermore, the immune effects of CRH can be antagonized by GABA receptor antagonists (Irwin et al., 1993b), which are known to abrogate the behavioral stress effects of CRH, suggesting an interplay between GABAergic receptor mechanisms and CRH in the regulation of behavioral and immune responses. Moreover, CRH receptor expression in the amygdala, but not in the pituitary adrenal axis, was linked to immune responsivity (Hauger et al., 1993); chronic administration of central CRH induced a marked downregulation of CRH receptor number in the amygdala, which was coupled with neuroimmune desensitization. Downregulation of CRH receptors has been measured in depression, and impairments of mood and immune homeostasis may be dependent in part upon functionally intact brain CRH receptors.

These experiments used doses of CRH as a pharmacologic probe to examine the links between brain and immunity. However, the question of whether CRH acts as an *endogenous* mediator of stress-induced immune suppression within the brain was not addressed. Hence, in collaboration with colleagues at the Salk Institute, an inescapable stress model was developed. Footshock stress was found to induce a biphasic alteration of NK activity; initial immune suppression was followed by immune enhancement after repeated administration of intermittent footshock (Irwin et al., 1990d). The role of CRH in

mediating such stress-induced immune suppression was investigated by using polyclonal antibodies to CRH. Central immunoneutralization of CRH antagonized the suppressive effects of footshock, and demonstrated for the first time that endogenous brain CRH was involved in the in vivo regulation of this distinct functional population of lymphocytes. Future studies are needed to determine whether these immune effects of central CRH are mediated via CRH1 versus CRH2 receptor mechanisms. Moreover, the translational implications of this work have yet to be realized. However, as CRH antagonists become available for clinical use, targeting this neuropeptide has the potential to reverse the immune declines found in humans who are undergoing severe stress or who suffer from major depression.

4. HPA effector mechanisms

CRH as a neuropeptide model of stress was also used to probe the links between the central nervous system and the peripheral immune system, and to define physiologically relevant effector mechanisms. Toward this aim, initial studies focused on the release of adrenocorticopic hormone (ACTH) and glucocorticoids following CRH, given that HPA axis activation occurs with stress and in vitro doses of glucocorticoids induce marked declines in cellular and NK immune responses. Whereas footshock stress was found to induce a robust decline in NK cell activity, pre-administration of peripheral doses of CRH polyclonal antibodies failed to antagonize these effects, even though stress-induced increases of ACTH and corticosterone were abrogated (Irwin et al., 1990d). This finding was consistent with prior work showing that neither adrenalectomy nor hypophysectomy was sufficient to antagonize the acute immune suppressive effect of stress in rats (Keller et al., 1983,1988), which implicated other effector pathways. Clinical observational studies in humans further suggested that HPA axis activation is generally unrelated to acute stress-induced immune suppression. For example, in women who are suffering from the stress of anticipatory bereavement, reductions of NK activity were found despite levels of cortisol that were comparable to non-bereaved controls (Irwin et al., 1988a).

5. Sympathetic effector mechanisms

Noradrenergic innervation of lympoid tissue is well-described, and lymphocytes express β-adrenergic receptors, mainly of the β_2 subtype as previously reviewed (Friedman and Irwin, 1997). In vitro studies had further shown that catecholamines and neuropeptide Y (NPY), a sympathetic neurotransmitter that is co-localized with norepinephrine in the sympathetic terminal, are capable of suppressing cellular and natural immune responses at physiologic levels (Friedman et al., 1995). Hence, we examined whether central nervous system activation of sympathetic outflow by either stress or the central administration of CRH coordi-

nated immune suppression. Initial studies demonstrated that blockade of autonomic outflow using the postganglionic blocker, chlorisondamine, abrogated CRH suppression of NK activity (Irwin et al., 1988b). The role of sympathetic activation and β_2-adrenergic receptor activation in mediating these effects was confirmed, as CRH induced immune suppression was antagonized by either chemical sympathectomy using 6-hydroxydopamine, administration of the non-selective β-adrenergic receptor antagonist propranolol, or pretreatment with the selective β_2 receptor antagonist butoxamine (Irwin et al., 1990b). Together, these findings were among the first to demonstrate the functional significance of noradrenergic innervation of the spleen in the in vivo regulation of immunity.

Clinical translational studies built upon these animal models and evaluated the role of sympathetic effector mechanisms in depression and chronic stress, as well as acute experimental stress. In observational studies, subjects with major depression or chronic stress were found to have reductions in the NK activity as compared to non-depressed and non-stressed controls (Irwin et al., 1991). Along with this immune alteration, both depressed and stressed subjects evidenced increases in circulating levels of NPY and in sympathetic responsivity to orthastatic challenge. Importantly, NPY levels were not impacted by orthostatic challenge, but rather showed static elevations in the depressed and stressed subjects, indicating that circulating levels of this neuropeptide serves as a tonic measure of sympathetic activity. Correlational analyses demonstrated that increases of NPY negatively correlated with NK activity, independent of clinical demographic factors and levels of catecholamines, implicating NPY is a key neurotransmitter associated with immune alterations in depression and stress in humans (Irwin et al., 1991).

Experimental studies further characterized the role of β-adrenergic receptor activation in mediating changes in immunoregulatory cell number and function. To elicit acute sympathetic stimulation, subjects participated in exhaustive aerobic exercise following pretreatment for one week with either the non-selective β-adrenergic receptor antagonist propranolol or the selective β_1 antagonist metoprolol (Murray et al., 1992). Before treatment, exhaustive exercise led to a marked lymphocytosis with greater increases in T suppressor/cytotoxic and NK cell populations, which have among the largest density of β-adrenergic receptors. In addition, exercise induced pronounced decreases of stimulated lymphocyte proliferation and increases of NK activity. However, one week of propranolol treatment blunted the exercise-induced changes in lymphocyte numbers and cellular immune function, whereas treatment with metoprolol did not alter the effects of exercise. Consistent with animal models, these experimental studies in humans confirmed that β_2-adrenergic receptor activation mediates stress-induced alterations in immunoregulatory cell traffic. Further studies have shown that β-adrenergic receptor signaling mediates acute changes in inflammatory responses and endothelial activation

(Goebel et al., 2000; Kuhlwein et al., 2001), along with increases in chemotaxis (Redwine et al., 2003). Together these data suggest that sympathetic activation potentiates the signaling and migration of immune cells to sites of inflammation or infectious challenge, with implications for athersclerosis and cardiovascular disease progression.

Recent studies have focused on the role of sympathovagal balance and vagal tone on innate immune system responses, which are important in combating microbial pathogens through expression of proinflammatory cytokines and upregulation of co-stimulatory molecules to induce adaptive T- and B-cell responses. Substantial evidence in animals has found that sympathetic effector mechanisms suppress proinflammatory cytokine expression, but real-time in vivo assessment of autonomic activity in relation to innate immunity has not been extensively examined in humans. Heart rate variability serves as a non-invasive method for assessing autonomic activity using spectral analytic approaches; spectral power in the high frequency (HF) band estimates vagal tone, and the ratio of power in the low frequency (LF) band to power in the high frequency band (i.e., LF/HF ratio) estimates sympathetic output. Hence, heart rate variability provides an in vivo measure of both sympathetic and vagal activity; assessment of these two autonomic outputs can not be captured by measurement of circulating catecholamines, which yields only a downstream pooled estimate of prior sympathetic activation without assessment of vagal output.

In these experimental studies involving cocaine dependent persons, acute cocaine was administered intravenously to induce marked increases in symapthovagal balance and decreases in vagal tone as estimated by heart rate variability (Irwin et al., 2007a). Cocaine also induced a profound decline in TLR-4 stimulated monocyte production of IL-6 and tumor necrosis factor-α (TNF) at the cellular level, and these changes were associated with individual differences in increases of sympathetic output and/or decreases in vagal tone in response to cocaine. In contrast, circulating levels of cocaine did not correlate with alterations in these innate immune responses. Hence, these data suggest that cocaine induces a dysregulation of sympathovagal balance, which in turn attenuates the innate immune response. These findings have implications for risk of bacterial infectious diseases, because TLR4 signaling initiates defense against bacteria in which subsequent expression of TNF and IL-6 mediates innate immune responses to recognize and eliminate polymicrobial infections (Miller et al., 2005), especially those due to gram-negative bacteria (Hoshino et al., 1999).

Investigating sympathetic and immune interactions has identified the critical role of sympathetic output in mediating immune cell traffic and a broad array of immune responses that impact immune competence, as well as inflammation. Pharmacologic strategies that target this endogenous biological modulator of the immune system hold promise, for example, in impacting infectious disease risk. Cole and colleagues have demonstrated that sympa-

thetic activation accelerates HIV replication and progression (Cole et al., 2001,2003); pharmacologic blockade of β-adrenergic receptors might be found to alter the course of HIV disease. In addition, increases in sympathetic output are well known to occur in aging (Irwin et al., 1991), and targeting adrenergic receptor activation in older adults has the potential to influence the decline of cellular immune responses, as well as the increases in inflammation that occur in this population at risk for infectious and inflammatory disorders. Similarly, it is possible that behavioral strategies that downregulate sympathetic output, or alternatively increase vagal tone, could have downstream effects on immunoregulatory cell mechanisms and potentially, for example, alter proinflammatory cytokine activity in older adults.

6. Sleep: a salient behavioral mechanism

Sleep is a dynamic behavioral state, which serves a role in the homeostatic regulation of sympathetic and neuroendocrine activity (Fig. 1). In contrast to other behavioral states that rely, for example, on subjective reports, the behavioral dynamics of sleep can be objectively quantified by polysomnography to provide an index of the amount and depth of sleep. Polysomnographic recording of sleep can be further utilized to identify changes in the electroencephalographic (EEG) brain activity across the night as defined by sleep continuity and sleep architecture measures. Sleep continuity is characterized by total sleep time, sleep latency and sleep efficiency; sleep latency is defined as the duration of time to fall asleep, and sleep efficiency is the percentage of total sleep time over the course of one's total time in bed. Sleep architecture is characterized by five stages of sleep: stages 1–4 and rapid eye movement (REM) sleep. The sleeping person transitions through these stages repeatedly during the night. Stages 1–4 together are called non-REM (NREM) sleep; stages 3 and 4 are termed slow wave sleep or delta sleep and are the deepest sleep. During REM sleep, brain activity appears similar to the waking state and is characterized by periodic eye movements and muscle atonia. The amounts and intensity of slow wave and REM sleep are important for sleep–wake regulation, as evidenced by rebounds in these variables following sleep deprivation (Irwin et al., 2002).

In a series of clinical observational studies that documented immune alterations in depressed patients, disturbances of sleep were found to be uniquely related to declines of NK activity, as well as increases in markers of inflammation (Irwin, 2002). For example, subjective sleep quality and insomnia complaints negatively correlated with NK activity in depression, whereas other depressive symptoms including somatization, weight loss, cognitive disturbance, or diurnal variation did not show a similar relationship (Cover and Irwin, 1994; Irwin et al., 2003a). Likewise, EEG studies reveal that disturbances of sleep continuity (e.g., prolonged sleep latency, declines of total sleep time) correlated with alterations of natural and

cellular immune function among depressed patients (Irwin et al., 1992c). Furthermore, Motivala and colleagues (Motivala et al., 2005) found that prolonged sleep latency and increases of REM density are associated with elevated levels of IL-6 and soluble intercellular adhesion molecule (sICAM) in depression, and fully account for the association between depression and IL-6. Finally, in primary insomnia patients who solely have chronic sleep disturbances, without co-morbidity for another psychiatric disorder (e.g., depression), alterations of cellular immune responses and inflammatory cytokine levels (e.g., IL-6) are found, which are comparable to the differences found in depression (Irwin et al., 2003a). Together these naturalistic data support the hypothesis that sleep disturbance has a role in the regulation of immune cells and their function.

The relationships between sleep and sleep disturbance on immune cell dynamics during the nocturnal period have also been systematically examined by characterizing sleep throughout the night, along with repeated measures of immune cell function and/or proinflammatory cytokine activity. In normal volunteers who show no evidence of subjective or objective disturbance of sleep, the nocturnal period is characterized by changes in a number of immune variables, including increases in NK activity, a shift toward Th1/Th2 cytokine production with relative increases in the production of the Th1 cytokine interferon-γ, increases in the production IL-6 and in circulating levels of IL-6, and increases in the expression of cellular adhesion molecules (e.g., macrophage associated antigen, Mac-1) (Redwine et al., 2000,2003,2004; Irwin et al., 2004). In contrast, among persons who have substantial disturbances of sleep such as a profound loss of slow wave sleep (e.g., patients with alcohol dependence in remission), dynamic increases in NK activity, Th1/Th2 cytokine production, and proinflammatory cytokine production are not found (Redwine et al., 2003). Hence, it is tempting to speculate that sleep promotes "restorative" functioning including greater immunologic activity with implications for immune competence, and that this dynamic function of sleep is impaired in patient populations who evidence abnormalities in either sleep continuity and/or sleep architecture (e.g., loss of delta sleep).

To understand further the role of sleep in the regulation of immunity, and whether sleep loss might account for alterations of immunity that have been found in patient populations, experimental approaches were employed. Modest loss of sleep during a single night (i.e., partial night sleep deprivation) is comparable to the kinds of sleep disturbance that is often reported in patients who are depressed or undergoing severe psychological stress. In addition, sleep deprivation of limited duration does not induce an activation of stress response systems such as HPA axis or sympathetic activation, which can occur with sleep loss that lasts beyond a single night (Redwine et al., 2000). In healthy volunteers, partial night sleep loss was found to produce a reduction in NK activity and lymphokine activated killer cell activity (Irwin et al., 1994,1996),

and in the ability of mononuclear cell to produce IL-2, which was due to alterations in the function of both monocyte and lymphocyte populations (Irwin et al., 1996). Importantly, most of these changes in immune responses are transient and fully normalize once normal volunteers undergo recovery sleep that is characterized by rebound increases of total sleep time and delta sleep. In contrast, among patient populations who have a deficit in delta sleep regulation with a failure to evidence homeostatic sleep recovery following sleep deprivation, the effects of sleep loss on sympathetic output and proinflammatory cytokine activity are potentiated with exaggerated increases in these outputs, which continue even after a night of recovery sleep (Irwin et al., 2004; Irwin and Ziegler, 2005). Such persistent dysregulation of autonomic and inflammatory mechanisms in patients who experience chronic, recurrent sleep loss may have pathophysiologic consequences with particular impacts on cardiovascular and inflammatory disorders.

Epidemiologic data implicate poor sleep as a predictor of chronic disease risk and cardiovascular mortality (Mallon et al., 2000; Kripke et al., 2002), and it is increasingly important to consider the consequences of sleep loss on inflammatory mechanisms. The risk of a wide spectrum of conditions including cardiovascular disease, arthritis, and diabetes mellitus is associated with activation of cellular signals that lead to the production and expression of IL-6 (Ershler and Keller, 2000). As noted above, we and others have found that experimental sleep loss can lead to increases in circulating markers of IL-6, TNF, and C-reactive protein (CRP) (Irwin et al., 2004; Meier-Ewert et al., 2004). We sought to clarify the functional basis for altered proinflammatory cytokine activity following sleep loss, and examined monocyte cellular production of IL-6 and TNF, along with analyzing the impact of partial night sleep deprivation on transcription of proinflammatory cytokine genes. Experimental sleep loss was found to induce a marked and transient increase in TLR4 stimulated monocyte production of TNF and IL-6 (Irwin et al., 2006). Similarly, sleep loss induced a more than threefold increase in transcription of IL-6 messenger RNA and a twofold increase in TNF messenger RNA. Additional analyses determined whether increased inflammatory gene expression might constitute one element of a more general genomic response to sleep deprivation as assessed by DNA microarray analyses and bioinformatics analyses. Indeed, altered expression of proinflammatory cytokine genes emerged along with enhanced expression of the circadian clock gene PER1 and multiple immediate early response genes, signal transduction mediators, and growth factor-related genes. Bioformatic analyses suggested that inflammatory response was mediated by the nuclear factor κB inflammatory signaling system (Irwin et al., 2006).

The translational implications of the link between sleep and inflammation are important at several levels. Sleep disturbance is common in many inflammatory disorders (e.g., rheumatoid arthritis), yet it is not known whether sleep loss leads to an exaggerated or more prolonged inflammatory

response in these patients. Additional consideration of the cellular signaling pathways that might mediate the effects of sleep loss on inflammation, including analyses of nuclear factor κB inflammatory responses are needed. Moreover, relevant studies are needed to determine whether morning elevations in cellular proinflammatory cytokine expression might have consequences for daytime levels, with impacts on other behaviors such as depressive symptoms, fatigue (see below) and pain. Finally, testing of interventions that target sleep and/or its biological consequences might identify new strategies to constrain inflammation and to promote health as people age.

7. Clinical translational implications

7.1. Cardiovascular disease

Measures of subchronic systemic inflammation are implicated as prognostic factors in patients with cardiovascular disease (Volpato et al., 2001). Given evidence that depression can lead to inflammation, it is possible that this is one mechanism that underlies the association between depression and mortality risk in patients with acute coronary syndrome. However, depression and inflammation likely combine in complex ways to influence coronary artery disease. Clinical studies suggest that chronic stress and depression augment innate inflammatory responses (Pike and Irwin, 2006; Irwin and Miller, 2007), leading to increases of CRP, IL-6, and the endothelial activation marker sICAM-1. Alternatively, systemic inflammation may give rise to symptoms of depression (as noted below). To examine these questions, we first characterized the impact of depression on markers of inflammation in patients with acute coronary syndrome, and found that co-morbid depression was associated with higher levels of sICAM-1 and with increases in levels of CRP, although the latter differences were primarily found in those patients not treated with statins (Lesperance et al., 2004). Statins are known to lower levels of systemic inflammation, and use of these medications appears to confer some benefit on depression related elevations in these markers.

A prospective study has also recently been carried out to confirm the negative impact of depression on cardiac prognosis in patients after acute coronary admission, and to investigate the relationships between depression and markers of inflammation in predicting subsequent cardiac events. In this study, 741 acute coronary syndrome patients who were assessed for depression and inflammatory markers approximately 2 months after discharge for acute coronary syndrome and were followed for major adverse cardiac events over 2 years (Frasure-Smith et al., 2007). Consistent with prior observations, depression as measured by severity of depressive symptoms or syndromal diagnosis was related to the occurrence of a major adverse cardiac event. In addition, an interaction between depression symptoms and CRP in predicting cardiac events was found. Men with low levels of depression and low levels of CRP evidenced low risk of major adverse cardiac events.

However, the presence of either depression or elevated CRP was associated with increased major adverse cardiac events, and men with both elevations in depression and CRP show similar increases in risk (Frasure-Smith et al., 2007). This profile of partially overlapping prognostic risk between depression and inflammation suggests that the impact of depression is not explained by inflammation, but raises the possibility that both risk factors could benefit from similar interventions. For example, interventions such as regular exercise, a Mediterranean diet, and antidepressants, combined possibly with statins may impact inflammation and could possibly treat depression in coronary artery disease patients. Dysregulation of other cytokine profiles may also contribute to mortality risk in cardiovascular disease populations; Redwine and colleague recently reported that a shift toward Th2 cytokine expression was associated with cardiac related hospitalizations and death over two years follow-up in patients with congestive heart failure (Redwine et al., 2007).

7.2. Infectious disease: herpes zoster

As noted in Section 2 of this review, prior studies of depression and immunity had primarily focused on non-specific measures of immunity, and the clinical relevance and significance of these immune alterations has been questioned (Stein et al., 1991). In an effort to address this gap, ongoing studies are examining cell-mediated immunity to varicella zoster virus (VZV), which is thought to be pivotal in determining the risk of herpes zoster (Levin et al., 2003). Herpes zoster or shingles results from reactivation of latent VZV and is characterized by a painful vesicular rash. The incidence of herpes zoster increases with age with more than half of all persons in whom herpes zoster develops being 60 years and older (Levin et al., 2003). The increase in incidence of herpes zoster correlates with a progressive age-related decline in circulating VZV-specific memory T-cells. Together these observations suggest that efforts to elicit increases in VZV-specific cell-mediated immunity might provide protection against herpes zoster. Recently, a large Department of Veterans Affairs cooperative study involving 38,546 older adults demonstrated that administration of a high potency Oka/Merck VZV vaccine (ZOSTAVAX) reduced the incidence of herpes zoster 51% and the incidence of postherpectic neuralgia by two-thirds; this protection correlated with the magnitude of boosting of VZV-specific cell-mediated immunity (Oxman et al., 2005). Given prior evidence that VZV-specific immunity is decreased in middle-aged adults (Irwin et al., 1998), a Depression Substudy is now prospectively analyzing differences in resting and vaccine stimulated VZV immune responses in depressed and non-depressed older adults in association with shingle risk. If the study hypotheses are confirmed, findings would have immediate public health implications in prioritizing depressed older adults for vaccination and/or providing access to booster vaccine doses.

Administration of varicella vaccine conferred substantial benefit for the prevention of herpes zoster, yet the risk was not eliminated and nearly one-half of older adults remained at risk for shingles (Oxman et al., 2005). Moreover, a number of older adults (e.g., those who are immunosuppressed) will not be eligible to receive this live-attenuated vaccine. Hence, we have pursued novel strategies to boost VZV immunity in older adults and examined the potential use of a behavioral intervention as an independent means of augmenting VZV-specific cell-mediated immunity, and of complementing vaccine induced immune responses (Irwin et al., 2003b,2007b).

Tai Chi, a traditional Chinese martial art, incorporates aerobic activity, relaxation, and meditation, all of which are reported to boost cell-mediated immune (CMI) responses. In addition, Tai Chi is a particularly attractive intervention for use in older people, who often have age-related limitations in their ability to tolerate even moderate-intensity exercise. A small controlled pilot study found that Tai Chi Chih (TCC), a westernized, standardized version of Tai Chi, boosted VZV-CMI (Irwin et al., 2003b), but conclusions were constrained by the small sample size and the use of a wait-list control condition. Moreover, the possible effects of TCC on immune responses to vaccination were not assessed.

A large clinical trial was recently conducted to compare the effect of TCC with that of health education (HE) on baseline VZV-specific T-cell immunity in older adults, and whether TCC might augment the increase in immunity to VZV induced by a licensed live attenuated varicella vaccine (VARIVAX) (Irwin et al., 2007b). The findings showed that TCC increased resting levels of VZV-specific CMI to a degree comparable with levels induced by varicella vaccine (VARIVAX). Moreover, the combination of TCC and varicella vaccine boosted VZV-CMI nearly 40%, to levels of VZV-specific CMI comparable with those previously observed in adults who were 30 years younger (an age at which the incidence and severity of herpes zoster are substantially lower).

The ability of TCC to increase resting levels of VZV-CMI may have broad implications. VZV-CMI measures primarily VZV-specific memory T-cells (CD41 CD45RO1 T-cells), and the capacity of TCC to increase the number of circulating VZV-specific memory T-cells may generalize to memory T-cells specific for antigens of other pathogens that cause severe disease in older adults. In addition, older adults often respond poorly to immunization, and TCC might improve the efficacy of other vaccines (e.g., influenza) in older adults, which would have further public health implications. Ongoing intervention studies are underway to examine the mechanisms of benefit and health promotion of this behavioral approach in older adults. Given the links between sleep and immunity, interventions are also targeting insomnia, which is highly prevalent in older adults; future studies will determine whether treatment of insomnia will restore homeostatic balance, with hypothesized effects on sympathovagal balance, increases of cellular immunity and decreases of inflammation.

8. Cytokines to behavior

Communication between the brain and the immune system does not flow only from the brain to the immune system, but also from the innate immune system to the brain. An emerging hypothesis generated from the findings of immune activation in depression was that cytokine abnormalities might contribute to depressive symptoms including disordered sleep and fatigue (Dantzer, 2001). Basic research in the neurosciences has shown that proinflammatory cytokines can signal the central nervous system, and possibly contribute to symptoms of insomnia and fatigue in humans. Several inflammatory mediators have been linked to altered central nervous system activity, including IL-1, IL-6, and TNF, and alterations in proinflammatory cytokines have been found in disorders with insomnia and fatigue, such as depression as previously reviewed (Irwin and Miller, 2007). Such results suggest that persistent unexplained insomnia or fatigue in certain patient populations could stem from an underlying long-term alteration in inflammatory biology.

Dysregulated production of proinflammatory has been reported during cancer treatment and attributed to the effects of chemotherapy or radiation. Previous studies by Bower have found elevated serum markers of proinflammatory cytokine activity and correlated alterations in T lymphocyte subsets in breast cancer survivors suffering from fatigue 3–5 years after the completion of therapy in the absence of any detectable residual disease (Bower et al., 2002,2003). Further studies have clarified the basis for aberrant cytokine levels in disease-free breast cancer survivors with persistent fatigue by analyzing the number and functional characteristics of leukocytes that produce proinflammatory cytokines (Collado-Hidalgo et al., 2006). Fatigued breast cancer survivors were distinguished from non-fatigued survivors by increased ex vivo monocyte production of IL-6 and TNF following TLR-4 stimulation, elevated plasma IL-1ra and soluble IL-6 receptor (sIL-6R/CD126), decreased monocyte cell-surface IL-6R, and decreased frequencies of activated T lymphocytes and myeloid dendritic cells in peripheral blood. These analyses help define specific molecular targets for interventions that ameliorate fatigue by addressing its inflammatory basis. Development of such therapies could markedly enhance quality of life in the significant fraction of breast cancer survivors that suffer from persistent fatigue.

A complex network of proinflammatory mediators is also triggered by alcohol dependence, and is thought to be involved in the development of disturbances of sleep architecture (e.g., increases of REM sleep) in these patients (Redwine et al., 2003; Irwin et al., 2004). As noted above, abnormal increases in circulating levels of proinflammatory cytokines have been found in alcohol dependence, which is coupled with severity of sleep disturbance. To further

investigate these relationships, repeated sampling of circulating levels of IL-6 and TNF was obtained before, during, and after nocturnal sleep in an effort to evaluate the temporal links between proinflammatory cytokine activity and disordered sleep. Consistent with the notion that cytokines have reciprocal effects on sleep, physiological elevations and individual differences in cytokines were found to temporally predict sleep continuity and sleep architecture measures (Irwin et al., 2004). For example, increases of IL-6 prior to the onset of sleep, but not during sleep, correlated with prolonged sleep latency; and increases of IL-6 during sleep, but not after the sleep period, correlated with increases in rapid eye movement (REM) sleep. These associations were reliably demonstrated across three separate nights, independent of the contribution of alcohol consumption histories, body mass index and, and education which can have effects on IL-6 and on sleep (Irwin et al., 2004).

Together, these correlative, observational studies in cancer survivor and in alcohol dependent populations, which link proinflammatory cytokine activity with fatigue and sleep, raise several relevant questions. If inflammatory cytokines are blocked, which aspects of fatigue and sleep improve and how clinically relevant is the improvement? Of note, a number of TNF receptor antagonist medications are all available commercially for the treatment of rheumatoid arthritis, and therefore are available for preliminary analyses of efficacy in patients with alterations in behaviors including insomnia, depression, or persistent fatigue. Indeed, 12 weeks of etanercept administration led to improvements in depressive symptom severity in 618 psoriasis patients (Tyring et al., 2006). Hence, building upon these observational data, future experimental data are needed to determine whether physiological elevations in markers of systemic inflammation mediate certain behavioral symptoms, and whether novel approaches that target relevant aspects of the immune response might show efficacy in the treatment of depression, insomnia, or fatigue.

9. Conclusions

The immune system is highly integrated with other physiological systems. It is sensitive to virtually every hormone, and sympathetic, parasympathetic, and sensory nerves innervate the organs of the immune system. In turn, the nervous, endocrine, and immune systems communicate bidirectionally through common hormones, neuropeptides, and cytokines. Hence, one conceptual theme of this review is that behavioral responses are key in the activation of neuroendocrine and autonomic pathways, which in turn modulate the immune system with implications for increasing susceptibility to a variety of diseases. On the other hand, communication between the brain and the immune system is reciprocal. Increasing effort is underway to define immune-to-brain communication pathways, which induce a cascade of cellular and molecular events in the central nervous system with potential behavioral consequences.

Acknowledgments

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