Section 1
Chapter 1

Introduction

Introduction to cancer symptom science

Charles S. Cleeland, Michael J. Fisch, and Adrian J. Dunn

More than 11 million people in the United States have a history of cancer, and more than 1.4 million new cases of the disease are diagnosed every year. Due to progress in the prevention and treatment of cancer, approximately 68% of patients now survive for at least 5 years after diagnosis; nonetheless, 18% will die, often after months of painful, progressive illness.[1]

The symptoms experienced by patients with cancer and even cancer survivors are well known to cause significant distress, affect the ability to function, and impair rehabilitation. Whereas many of these symptoms are the result of disease, it is increasingly recognized that pain, neuropathy, fatigue, sleep disturbance, cognitive dysfunction, and affective symptoms can also be caused by the treatments for the cancer. Treatment-related symptoms may persist for weeks, months, or years and may worsen, even when the cancer improves; they can limit vocational activity and inhibit social recovery.

In many cases, cancer can be managed much like other serious chronic diseases – thus extending for many years the need for continued treatment accompanied by the frequent monitoring and managing of treatment-related symptoms. And, as patients survive cancer for increasingly longer periods, persistent residual treatment-related symptoms are becoming more prevalent and pose an increasing barrier to the resumption of predisease functioning. Treatment-related symptoms can directly affect survival if they become so severe that patients abandon potentially curative therapies. Having the ability to control or even prevent such symptoms would be of potential benefit to thousands of cancer patients and survivors.

Symptoms and symptom burden

A symptom is a sensation or perception of change related to health function. Symptoms, such as fatigue, pain, and nausea, may be classified based on their severity and perceived impact on function. A symptom that leads to a diagnosis is called a cardinal symptom. In a medically correct sense, a symptom is a subjective report.

In contrast, a sign – such as elevated blood pressure or abnormal appearance of the retina – is objective evidence of the presence of a disease or disorder. A symptom can thus more simply be defined as any feature that is noticed by the patient, whereas a sign is noticeable by others; it is not necessarily the nature of the sign or symptom that defines it, but who observes it. The same feature may be noticed by both doctor and patient, and so is at once both a sign and a symptom. Some events, such as pain, can only be symptoms. Other indicators, such as a blood cell count measured by a doctor or a laboratory, can only be signs.

Moderate and severe cancer-related symptoms greatly affect a patient's quality of life and ability to function, collectively creating a "symptom burden" upon the patient that can be thought of as the subjective counterpart of the tumor burden caused by the disease. Anyone who has or has had cancer or who treats patients with cancer knows that multiple symptoms clearly coexist and that symptoms may exacerbate the severity of one another (eg, pain is often linked with affective disturbance, sleep problems, difficulties with concentration, and fatigue), yet only recently has serious attention been paid to this fact. And despite broad appreciation for the distress caused by cancer-related symptoms, relatively little is known about how biobehavioral mechanisms may cause or contribute to the emergence of symptoms or symptom clusters (two or more symptoms that co-vary in onset and severity) from cancer or cancer therapy.

The possibility that many symptoms are induced by a common mechanism finds its expression in the characteristics of animal models of sickness behavior, which resemble the expression of symptoms in patients with cancer.[2–5] "Sickness behavior" refers to a constellation of behavioral and physiological

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responses observed in animals after administration of inflammatory agents or specific proinflammatory cytokines.[6,7] Findings in animals need to be strongly linked to symptom expression in cancer patients, and the study of symptoms in cancer patients needs to inform the development of animal models. If such associations could be established and specific mechanisms be identified, we could manage multiple symptoms via their underlying mechanisms rather than by the use of empirical treatments for individual symptoms, such as stimulants for fatigue or opioids for pain.

A better understanding of symptom mechanisms may bring a melding of treatments directed at tumor burden with those that reduce symptom burden. Ultimately, the goal in the treatment of cancer is to achieve a clinical response that offers the best quality of remission for the longest period.[8] This is especially important for patients with cancer that is currently incurable – where survival time has increased but quality of life is often diminished by aggressive therapy that causes intolerable symptoms. The development of new, targeted therapies represents an opportunity to reduce the burden of typical chemotherapy-induced side effects at the same time that disease control improves. However, these newer agents also bring novel side effects that will need further exploration and management to reduce the symptom burden and functional disturbance of patients who require therapy for malignancy.

The emerging science of symptom research

The emergence of a field of cancer symptom science – the inspiration for the creation of this book – in some ways parallels the types of collaboration that must be developed to gain a scientific understanding of a disease: the biological and behavioral aspects of the disease have to be understood, ways of measuring the prevalence and severity of the disease must be identified, existing treatments have to be tested to determine whether they are effective against the disease, and new treatments must be developed. When a new disease emerges, methods for its prevention and treatment do not yet exist. The research required to understand its biology, its behavioral ramifications, and the best way to treat it is not in place. Investigators must be attracted to the area, disciplines must talk to each other to develop appropriate methods of research, and investigators must be trained and funded. If hypotheses about the genesis of symptoms can be formulated and tested, those that withstand empirical tests should lead to the proposal of novel treatment methods.

The need for new approaches to symptom management in cancer is well recognized. The Institute of Medicine of the National Academy of Sciences lists the control of pain due to cancer as one of the top 20 health care priorities for improving health care.[9] A report of the National Cancer Advisory Board of the Institute of Medicine[10] called for a significant increase in symptom-directed research, noting that the feasibility of symptom-control research has been demonstrated. That report cited a broad range of recent advances, including the growing acceptance of subjective patient reports about symptoms as reasonable measures in the conduct of clinical and laboratory research. New investigational methods present unique opportunities to understand the biology underlying symptom expression and severity. Emerging methods in longitudinal modeling of symptom patterns, genetic screening (genomics), and longitudinal assays of the relationship between symptoms, cytokines, and neurotransmitters (proteomics) should provide information about patient–environment and treatment–environment factors that facilitate or inhibit symptom expression. Functional and molecular imaging methods should help us understand the cortical representation of symptoms and the specific molecules that are associated with cancer-related fatigue, pain, cognitive impairment, and other nonspecific symptoms.

The purpose of this book

The editors are pleased to offer *Cancer Symptom Science* as a resource for those interested in the goal of preventing or reducing the symptom burden of cancer. The overarching aim of this volume is to collect the developing threads of new approaches to understanding cancer-related symptoms and to illustrate how diverse areas of science can share findings that will stimulate novel approaches to symptom management. We offer contributions from component disciplines that are now poised to make major contributions to understanding the biobehavioral basis of symptoms and to test, in both preclinical models and clinical trials, new agents that may have a broad spectrum of effects on multiple symptoms simultaneously. Our chief aspiration in presenting this book is to promote

an interdisciplinary research effort that will provide a framework for:

- merging behavioral and biological disciplines to clarify the mechanisms of symptom evolution;
- developing animal models that parallel the behaviors of people with symptoms from cancer or its treatment;
- incorporating new technologies (eg, genetics, protein measurement, and functional and molecular imaging) that have been applied to other biological problems;
- testing potential novel agents for symptom control in both preclinical studies and clinical trials with cancer patients;
- developing new statistical models to integrate longitudinal symptom reports with multiple biological data points obtained during clinical studies; and
- promoting cross-disciplinary discussions that will create interdisciplinary-minded thinkers and expand the investigator base for sustaining this type of research.

Whatever the potential mechanistic basis of symptoms and their management will be, the interdisciplinary approach to understanding symptoms may look very much like a combination of the specific approaches presented in the following chapters.

We are hopeful that the synergy between the various disciplines described in the next chapters will inspire new ways to prevent the development of symptoms and to develop new or enhanced treatment methods for the symptoms of cancer and cancer treatment. The target of all of these efforts is the ultimate improvement in patient functioning, stress level, satisfaction with and willingness to endure therapy, and quality of life, both during and after cancer treatment.

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Section 1 Chapter 2

Introduction

Researching the mechanisms underlying the symptoms of patients with cancer

Adrian J. Dunn

The overarching goals of the science of symptom research are to prevent the development of symptoms and to establish new or enhanced treatment methods for the symptoms of cancer and cancer treatment, which may in turn lead to improvement in patient function, stress level, satisfaction with and willingness to endure therapy, and quality of life both during and after cancer treatment. To design treatments for the symptoms experienced by patients with cancer, it would be extremely useful to know the underlying mechanisms of those symptoms. In many areas of medicine, animal models have proven useful for suggesting underlying mechanisms of diseases and for testing appropriate therapies.

In this chapter we briefly discuss the theories underlying the use of animal models in cancer symptom research. Chapter 3 builds on this foundation with a review of animal research that may be appropriate for modeling the symptoms associated with cancer and its treatment.

The rationale for animal models

Using animal models in research

In principle, animal models can be used to mimic certain disease states, to identify potential underlying mechanisms and to test potential therapies – pharmacological, surgical, or otherwise. The primary rationale for using animal models is that certain experimental procedures are difficult to perform or would be considered unethical to perform in humans. Most often the justification is that the measurement of some important variable is too intrusive to measure in humans, or that a proposed experimental therapy carries unknown risks. In the most common examples, a drug known to affect a metabolic process may be tested in animals for its efficacy and/or to reveal unforeseen, unacceptable, or toxic side effects.

Animal models can have limited validity. For example, a treatment that works in rats may not work in humans in the same way and may induce unforeseen side effects. In general, animal models work best when the method for inducing the model is related to the underlying cause of the disease. This may not be too difficult when the underlying cause of the disease is known or suspected, but may be particularly difficult in the case of affective symptoms, especially symptoms like depression or psychosis. Do we really know that a rat or a mouse can experience depression as humans do? Assuming a rat can become psychotic, how would we recognize the psychosis?

Developing appropriate animal models

The most successful animal models have been developed on the basis of the disease state of interest. For example, in studies of Parkinson's disease, it was learned that the disease was associated with the death of certain neurons in the brain that use the neurotransmitter dopamine. Accordingly, dopamine depletion was induced in experimental animals using the neurotoxin 6-hydroxydopamine to create a model for Parkinson's disease. This resulted in the use of L-DOPA (levodopa), a precursor for dopamine, to ameliorate the depletion of brain dopamine, first in rats and later in humans.

Another example would be the use of methylphenidate (Ritalin®) to treat attention deficit hyperactivity disorder (ADHD) in children. Experiments showed that when rats were treated with the neurotoxin 6-hydroxydopamine, which depletes dopamine in the brain, the rats became hyperactive. This result was considered paradoxical because activity normally is increased by drugs that *stimulate* dopamine release, such as amphetamines. Also paradoxically, the hyperactivity in rats could be reversed by treatment with amphetamines and related drugs.[1] The changes pursuant to 6-hydroxydopamine treatment most likely

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occurred because the numbers of postsynaptic receptors for dopamine were upregulated (sensitized) by the 6-hydroxydopamine treatment in response to the lack of dopamine – the bodily mechanisms presumably attempting to normalize the system. Subsequently, amphetamine-like drugs, such as methylphenidate, were tested in children diagnosed with ADHD to enhance dopaminergic activity. This treatment has proven to be very successful in many patients, although not all patients respond appropriately. The most likely reason that this model was successful is that the neurotoxin-treated rat exhibited changes that resembled those in the human disease.

With respect to animal models, it is important to distinguish between an animal model and an animal test. A *model* is a procedure used to induce a state in the animal that resembles the disease to be studied. A *test*, however, is a procedure that can be used to detect signs or symptoms of the human disease (preferably quantifying them). For example, in the case of depression, most animal models have relied on chronic stress paradigms, because depression is often preceded by a stressful life event. On the other hand, *tests* for depression would include procedures such as the forced-swim test or the tail-suspension test, which have been used in experimental animals to assess depression-like activity or antidepressant efficacy.

Animal models and the mechanisms of cancer symptoms

It has been argued that the most appropriate model for the symptoms experienced by patients with cancer is so-called sickness behavior, which includes hypomotility (lethargy), hyperthermia, hypophagia (anorexia), decreased curiosity (for example, exploring new things), decreased libido, and increased time spent sleeping. "Sickness behavior" is a term coined by Benjamin Hart in a review in which he argued that the behavior of sick animals (and humans) was not just a nonspecific set of symptoms, but was a defensive strategy.[2] He wrote: "The behavior of a sick individual is not a maladaptive and undesirable effect of illness but rather a highly organized strategy that is at times critical to the survival of the individual if it were living in the wild state."

In fact, Hart was not the first to recognize the existence of sickness behavior. Several decades earlier, Hans Selye, then in medical school in Prague, noted that patients displayed certain symptoms that did not appear to reflect the specific aspects of their particular illness. He subsequently wrote: "Just look around and examine sick people. They are all indisposed, they look tired, have no appetite, gradually lose weight, they do not feel like going to work, they prefer to lie down rather than to stand up. Today, we would say they show non-specific manifestations of disease. They all present a syndrome simply indicative of being ill. That is why I baptized this state that so attracted my attention as 'the syndrome of just being sick.'"[3]

Selye and Hart both noted the similarities between sickness behavior and a variety of illnesses, but Hart's concept that sickness behavior was adaptive clearly indicated that whereas nonspecific symptoms did exist, some of the behaviors were indeed adapted to the specific problems presented by the disease. Thus sickness behavior is adaptive in the sense that at least some of the specific behaviors expressed may be specific for the disease. For example, if increasing body temperature would help to fight the disease, the body may invoke a fever, thus inhibiting the reproduction of certain viruses and enhancing the immune system's ability to kill the virus. A good example of the adaptability of sickness behaviors is found in the realm of sexual behavior, which is inhibited in sick females but not in males.[4] A sick female would not be well served by becoming pregnant, because this would place major demands on her body and very likely impair the growth and development of the fetus. On the other hand, males have little to lose, and sexual activity may enable the transmission of the males' genes.

Sickness behavior and inflammatory cytokines

Most or all of the sickness behaviors are induced when humans or animals are infected with viruses or other pathogens. Recently, there has been much focus on cytokines as mediators of sickness behavior, because infections and tissue damage induce a cytokine cascade involving the production of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, among others. In patients acutely ill from viral infections, Vollmer-Conna et al.[5] found that circulating concentrations of IL-1β and IL-6 spontaneously released from peripheral blood mononuclear cell cultures were consistently correlated with reported manifestations of a cluster of symptoms reflecting acute sickness

behavior, including fever, malaise, pain, fatigue, mood, and poor concentration.

Administration of cytokines to animals has induced a number of physiological and behavioral responses. These include changes in body temperature[6] and activation of certain endocrine systems, most notably the hypothalamic-pituitary-adrenal axis. Behavioral effects can be profound, including decreases in activity, feeding, exploration, and social behavior; increased sleep; and impairment of cognitive behaviors.[7,8] Neurotransmission in the brain is also affected and may underlie the endocrine and behavioral changes.[9] Administration of endotoxin (lipopolysaccharide, LPS) induces the synthesis of IL-1, IL-6, TNF-α, interferon (IFN)-γ, and perhaps other cytokines.

Particular attention has been focused on IL-1, because administration of this cytokine induces sickness behavior in several animal species, as further discussed in Chapter 3. Peripheral administration of IL-1 in animals has been associated with a variety of classic sickness behaviors, including increased sleep[10] and decreases in general activity,[11] feeding,[11,12] exploration of the environment,[13–15] social interactions,[16] and sexual activity.[17] (For reviews of the effects of IL-1 on behavior, see Dantzer et al.,[16] Kent et al.,[18] and Larson and Dunn.[8]) In addition, IL-1 affects memory[19] and motivation.[20]

Cancer symptoms and inflammatory cytokines

The behavioral activity of cytokines raises the possibility that cytokines secreted in cancer patients undergoing therapy may be responsible for some of the adverse neurobehavioral responses these patients experience.

It is well known that symptoms and increases in specific proinflammatory cytokines, primarily IL-1, IL-6, and TNF-α, are produced by both disease and treatment. Recent studies of rheumatoid arthritis, Crohn's disease, and depression have suggested that inflammation plays a central role in the production of multiple symptoms in diseases other than cancer, and that reduction of inflammation by targeted cytokine therapies produces amelioration of pain and other symptoms.[21–23] What is not known is whether these cytokines actually cause the emergence of symptoms and/or symptom clusters, and accordingly, whether modulation of these cytokines could affect the prevalence and severity of symptoms that cancer patients experience. This knowledge would support the development of symptom management strategies based on underlying symptom mechanisms rather than on the use of empiric treatments. (Bisphosphonates for bone pain and erythropoietin for fatigue and anemia are examples of mechanism-based treatments; the use of stimulants for fatigue and opioids for pain are examples of empiric treatments.)

A popular hypothesis is that excess IL-1 is responsible for inducing depressive illness, because depressed patients typically exhibit many sickness behaviors. However, this theory is controversial because, whereas early reports from Maes' laboratory indicated that stimulation of macrophages obtained from depressed patients stimulated with LPS *in vitro* showed increased secretion of IL-1,[24] subsequent studies have not demonstrated consistent increases in circulating concentrations of IL-1 (see Chapter 9).

Conclusion

The mechanisms underlying the production of symptoms in cancer are likely to be rather complex and may well differ among populations of patients; they would almost certainly depend on the organ(s) affected and the nature of the cancer. Animal models of cancer-related and cancer treatment-related symptoms may suggest a direction for future programmatic research into the mechanisms of symptoms. Careful description of cancer-related symptoms and correlation of these symptoms with clinical laboratory data, coupled with both laboratory and clinical research studies, is an important direction for future research. Clinical research needs to be complemented by animal and *in vitro* studies that directly examine cytokine dysregulation caused by cancer and cancer therapies, and agents that attenuate the inflammatory consequences of cancer therapies should be investigated. Such studies could lead to the control and possibly even the prevention of individual or clusters of cytokine-related symptoms.

The next chapter by Zalcman et al. reviews the research that has been performed using animal models that may be appropriate for modeling the symptoms associated with cancer and its treatment. Chapters 4–15 offer paired discussions of animal and clinical research for each of six symptoms commonly experienced by patients with cancer: pain, cognitive impairment, depression and affective impairment, fatigue, appetite loss and cachexia, and sleep disorders.

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Section 1
Chapter
3

Introduction

Cytokines and sickness behavior: a model for cancer symptoms

Steven S. Zalcman, Randall T. Woodruff, Ruchika Mohla, and Allan Siegel

The term "sickness behavior" refers to a series of behavioral and physiological changes that occur after exposure to an inflammatory or infectious agent, or after administration of recombinant proinflammatory cytokines.[1] Symptoms of sickness behavior include social withdrawal, anhedonia, cognitive impairment, anorexia, fever, and other symptoms. Behavioral changes associated with sickness behavior are transient in nature and serve adaptive purposes that help the individual mount an effective immune response.

Considerable attention has focused on the role of centrally acting cytokines in mediating sickness behavior. As might be expected, abnormal increases in cytokines appear to result in psychopathological outcomes. Indeed, sickness behavior and clinical depression (among other psychiatric disturbances) are evident in patients receiving cytokine therapy.[2] Increased proinflammatory cytokine activity has been implicated in the etiology of depression, schizophrenia, and other psychiatric disorders.[3]

Cancer-related symptoms are strikingly similar to the symptoms associated with cytokine-induced sickness behavior.[4] On the basis of this observation and coupled with evidence that behavioral disturbances in patients with cancer may occur coincident with abnormal increases in proinflammatory cytokines,[5] it has been suggested that common cytokine-related signaling pathways underlie sickness-related and cancer-related symptoms.[4,6] In this chapter, we will discuss similarities between cancer-related symptoms and sickness behavior, and we will examine potential common mediators and mechanisms, including proinflammatory cytokines and subsequent interactions with neurotransmitter and molecular signaling pathways.

Cancer-related symptoms

Cancer-related symptoms refer to physical and psychiatric manifestations produced by the disease process or treatment (including chemotherapy, radiotherapy, immunotherapy, and surgical procedures).[7] Cancer-related symptoms may be categorized as physical, cognitive, or affective. Physical symptoms include fatigue, pain, cachexia, gastrointestinal difficulties, and shortness of breath. Cognitive symptoms include memory deficits and impaired concentration. Affective symptoms include depression, irritability, and anxiety.

Symptoms may be directly or secondarily related to the disease process. For example, the pain induced by cancer or its treatment adversely affects a patient's mood and level of activity.[6] Multiple symptoms are typically present and may occur in clusters, such as the often-seen co-occurrence of pain, fatigue, and depression.[8,9] It has been suggested that analyses of symptom clusters can shed light on the extent to which common biological mechanisms underlie given symptoms.[10] However, there are disparities across studies about the extent to which specific symptoms cluster together. This is likely related to differences in the way in which symptoms are categorized, the diagnostic instruments used, and the heterogeneous nature of patient populations.[8] Despite these differences, investigators have observed that symptoms comprising cancer-related clusters are also characteristic of sickness-related behaviors.[4,11] Thus, insight into sickness behavior and the biological mechanisms underlying it could shed important light on mechanisms underlying cancer-related symptoms.

Sickness behavior

A series of alterations in neural and behavioral activity occurs in response to immunological challenge. Neural alterations serve to regulate the ongoing immune response (Figure 3.1).[12] For example, alterations of hypothalamic monoamine activity[12,13] are induced in sites mediating sympathetic outflow to immune organs,[14,15] which, in turn, modulates the

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ongoing response.[16] The behavioral changes, collectively referred to as sickness behavior, help the individual mount an effective immune response.[17]

Animal models of endotoxin and cytokine challenge

Sickness behavior has been studied extensively in animals by the use of endotoxin (lipopolysaccharide, or LPS) challenge and administration of proinflammatory cytokines. LPS, a component of the cell wall of gram-negative bacteria (eg, *Escherichia coli*, *Salmonella*), is released when bacteria are lyzed. In animal models, LPS is injected in purified form to induce a series of immunological, physiological, and behavioral changes that are characteristic of gram-negative bacterial infections. LPS challenge induces macrophage and endothelial cell production and the release of proinflammatory cytokines, notably interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ. LPS also induces an increase in proinflammatory cytokine activity in the brain.[18,19] Cytokines in turn stimulate the production of prostaglandins and leukotrienes. This cascade of events results in inflammation, fever, and behavioral alterations. The peripheral and central actions of cytokines released during the individual's response to an infectious or inflammation-inducing agent, among other factors,[20] likely mediate these behavioral changes. Similarly, administration of exogenous cytokines induces signs of sickness behavior.

Symptoms of sickness behavior

A range of behavioral changes, reminiscent of cancer-related symptoms, is induced by LPS challenge. Behavior changes include fatigue, depressive-like activity (including hypoactivity, social withdrawal, and anhedonia), cognitive difficulties, lack of appetite, altered response to predators, and sleep disturbances.[17] Such sickness-related behaviors are adaptive in nature. For example, depressive-like activity decreases metabolic demands that are otherwise taxed by increased immune activity and limits exposure to pathogens and predators, which could result in additional infection. Reduction in food consumption helps to deprive pathogens of nutrients. It should be emphasized that these behavioral changes are transient; persistent changes would be expected to result in psychopathological outcomes.[17]

Cytokines and sickness behavior

There is a striking overlap between cancer-related symptoms and sickness behavior. For example, classic symptoms of sickness behavior, such as fatigue, cognitive impairment, lack of appetite, depression, and pain, are evident in patients with cancer. It has been well established that proinflammatory cytokines induced in the periphery and in the brain during the host response to infection act as important mediators of sickness behavior. In patients with cancer, there is also evidence that symptoms occur coincident with increases in proinflammatory cytokines.[5] For example,

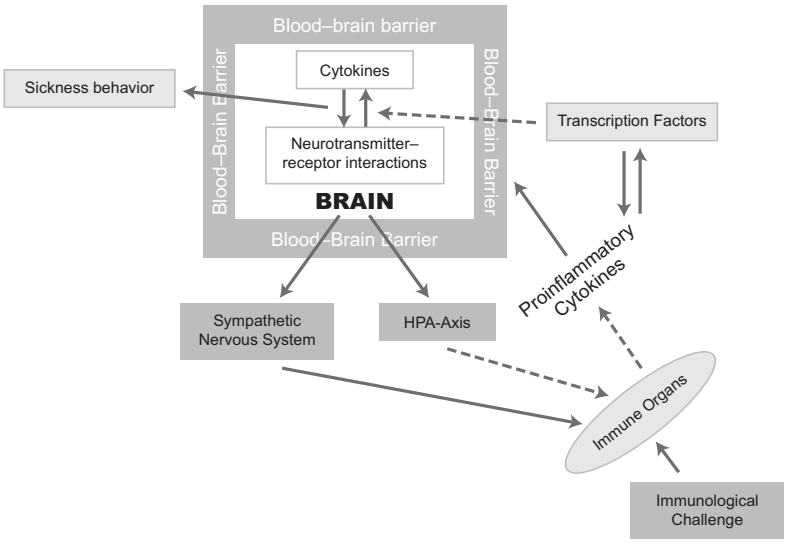

Figure 3.1. A schematic illustration of neuroimmune interactions. Alterations in peripheral and brain cytokine activity occur after immunological challenge. Cytokines may gain entry into the brain via transport across the blood–brain barrier or through circumventricular organs. Cytokines may also activate afferent nerves, which in turn alter brain activity. Immune-to-brain signaling serves to modulate activity in brain regions that mediate sympathetic outflow to immune organs and to stimulate HPA-axis activity. Cytokine–neurotransmitter and molecular interactions also underlie adaptive behavioral changes that are characteristic of sickness behavior.

depressive-like activity and cognitive impairment can be induced by injections of proinflammatory cytokines; similarly, proinflammatory cytokines have been implicated in the etiology of clinical depression (which develops in a subset of cancer patients receiving cytokine therapy), schizophrenia, and other psychiatric disorders.[1,3] In patients with metastatic colorectal cancer, increases in IL-6, TNF-α, and transforming growth factor-α have been shown to be correlated with increased fatigue, loss of appetite, reduced emotional and social functioning, and worsening performance status.[21]

In this section, we discuss representative overlapping behavioral alterations that are characteristic of sickness behavior and cancer-related symptoms, along with suggested underlying cytokine-related mechanisms.

Reduction in food intake

Reduced food consumption is a common consequence of illness, including cancer, and occurs after exposure to a variety of immunological challenges. For example, marked reductions in food consumption are induced in response to LPS challenge.[17,22,23] Administration of proinflammatory cytokines that mediate the host's response to LPS also results in a reduction in food intake.[24–26] Central microinjections of IL-1β into the ventromedial hypothalamus potently reduce food consumption in rats, indicating that this brain region may play a fundamental role in mediating the suppressive effects of IL-1 on feeding.[27] Of further importance, IL-1-induced anorexia activity and reductions in food consumption were prevented by pretreating rats with a serotonin synthesis inhibitor, suggesting that these effects are mediated by alterations in serotonergic mechanisms.[28] However, Swiergiel and Dunn[29] failed to find evidence in ad lib fed mice for the involvement of serotonin in IL-1-induced or LPS-induced reductions in milk intake.

Other cytokines, including IL-6, TNF-α, and IFN, also decrease food consumption, although their effects are less potent and are more dependent upon their route of administration.[1,30–32] Despite the parallels between LPS-induced and IL-1-induced reductions in food intake, combined antagonism of IL-1, IL-6, and TNF-α is required to attenuate the anorectic effects of LPS.[23] It should also be mentioned that treatment with a nonsteroidal anti-inflammatory drug (NSAID), which inhibits cyclooxygenase-2, attenuated body weight loss that was induced in mice treated with concanavalin A and in rats administered carbon tetrachloride.[33] These findings provide support for the use of NSAIDs, which have been employed to treat cachexia in cancer patients.

A significant number of patients with AIDS experience cachexia and reductions in food intake. HIV-related abnormalities are not due to the virus itself because neurons are not infected with the virus. Instead, it is thought that interactions among several factors are involved. These factors include viral elements (notably the HIV-1 viral envelope glycoproteins gp120 and Tat), and the induction of inflammatory cytokines secreted by infiltrating microglia. The latter occurs subsequent to the binding of gp120 to a receptor on glial cells,[34] which in turn stimulates production of various substances, including proinflammatory cytokines (eg, IL-1β). In rats, single intracerebroventricular injections of gp120 result in several neural and behavioral alterations, including reduced intake of standard laboratory chow.[35–39] It has been suggested that IL-1β is the principal mediator of gp120-induced effects, because pretreatment with IL-1 receptor antagonist (IL-1RA) blocks certain gp120-induced reductions in food intake.[35] IL-1RA selectively binds to the IL-1 type I receptor (IL-1RI) with the same affinity as IL-1β; thus, it has been concluded that this effect of gp120 is mediated centrally via IL-1RI. Further, the effects of acute gp120 administration on food intake are not related to alterations of central TNF-α.[36] In contrast with its modulatory effects on food intake, intracerebroventricular microinjections of IL-1RA do not block gp120-induced reductions in open-field activity.

As mentioned above, combined antagonism of proinflammatory cytokines, rather than antagonism of a given proinflammatory cytokine, is required to attenuate LPS-induced anorexia. Thus, the extent to which a given cytokine contributes to reductions in food intake after immune activation varies across different immunological challenges. It may also be concluded that a cytokine may play an important role in mediating the effects of an immunological challenge on food intake without having pronounced effects alone.

Psychiatric abnormalities

Direct evidence linking cytokines with sickness behavior and psychiatric abnormalities derives from studies using immunotherapy to treat various malignancies (and other illnesses).[2] In these studies, patients receive