CHAPTER

54 Stress, Negative Emotions, and Inflammation

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Abstract

Chronic low grade inflammation is a core pathophysiological process that may be involved in many age-related diseases. Elevations in circulating markers of inflammation have been associated with frailty and disability, osteoporosis, certain cancers, cardiovascular disorders, type II diabetes, rheumatoid arthritis, and Alzheimer's disease. Importantly, stress and negative emotions appear to promote the production of inflammatory mediators, providing a physiological mechanism by which negative psychological states may impact health. This chapter reviews the basic physiological processes of inflammation, the relationships among stress, negative emotions, social relationships, and inflammation, and the behavioral and physiological pathways linking stress, emotions, and inflammation.

Keywords: inflammation, Interleukin-6, C-Reactive protein, glucocorticoid resistance, stress, depression, caregiving, social support, social conflict, marriage, health behaviors, chronic disease, psychoneuroimmunology

Stress and negative emotions are daily occurrences that have psychological implications, but also clear endocrine and immune consequences. As such, these affective responses provide a window by which the external environment can influence the individual's physiology. Furthermore, increasing evidence suggests a bi-directional relationship between emotions and physiological systems, such that endocrine and immune changes may also modulate emotional responses. Of special interest for social neuroscience, inflammation, a component of immune function, may be a key physiological mediator of the impact of stress and negative emotions on health.

Chronic low-grade inflammation is a core pathophysiological process that may be involved in many age-related diseases. Elevations in circulating markers of inflammation have been associated with frailty and disability, osteoporosis, certain cancers, cardiovascular disorders, type II diabetes, rheumatoid arthritis, and Alzheimer's disease (Maggio, Guralnik, Longo, & Ferrucci, 2006). Importantly, stress and negative emotions appear to promote the production of inflammatory mediators, providing a physiological mechanism by which negative psychological states may impact health. The current chapter reviews the basic physiological processes of inflammation, the relationships among stress, negative emotions, social relationships and inflammation, and the behavioral and physiological pathways linking stress, emotions, and inflammation. Throughout the chapter, empirical human studies are emphasized.

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Acute Inflammation: An Essential Response to Infections and Injuries

Inflammation is an essential immune response triggered by infection and injury. It is the initial, automatic, and nonspecific reaction of the innate immune system that occurs upon exposure to an antigen—a substance foreign to the host's body. Inflammation promotes the destruction and clearance of pathogens and initiates wound healing, enabling the body to cope with a range of insults, from viral infections to allergic reactions to cutaneous wounds. This process is enacted primarily by cytokines; soluble proteins that provide an intercellular signal to recruit and activate other immune cells to the affected area.

Cytokines are produced mainly by immune cells such as monocytes, macrophages, lymphocytes, and endothelial cells, but they are also secreted by non-immune cells such as osteoblasts, intestinal epithelial cells, adipocytes, and vascular smooth muscle cells. Proinflammatory cytokines, such as interleukin-6 (IL-6) or tumor necrosis factor-α (TNF-α), promote a state of inflammation while anti-inflammatory cytokines, such as interleukin-10 (IL-10), decrease the production and function of proinflammatory cytokines, thereby regulating the immune response to antigens (Parham, 2004). In addition, cytokines may be classified as Th1 type or Th2 type. Th1 cytokines are associated with the proinflammatory response, which involves killing intracellular invaders. As prolonged Th1 response may result in tissue damage, the Th2 response counteracts this, promoting anti-inflammatory activity. Furthermore, some cytokines have both proinflammatory and anti-inflammatory properties. For example, IL-6 promotes local inflammation but also restrains inflammatory response by suppressing TNF-α and interleukin-1β (IL-1β) production, increasing IL-1 receptor antagonist and soluble TNF receptor p55, and by stimulating production of cortisol, a potent anti-inflammatory hormone (Tilg, Dinarello, & Mier, 1997).

Proinflammatory cytokines trigger the release of acute-phase reactants by the liver. Plasma concentrations of positive acute-phase proteins increase in response to inflammation, while negative acute-phase proteins decrease in response to inflammation. Positive acute-phase reactants, such as CRP and serum amyloid A, play a role in the inflammatory process, engaging in processes such as opsonization of antigens (flagging an antigen as a target for phagocytosis) or recruiting immune cells. Negative acute phase reactants are important carrier and metal-binding proteins (Gabay & Kushner, 1999).

Interleukin-6, TNF-α, and C-reactive protein (CRP) are the main inflammatory mediators that have been studied in relation to stress and depression in humans. Interleukin-1β is another important proinflammatory cytokine, but is harder to detect in plasma of healthy individuals. Figure 54.1 provides an overview of the component of the innate involved in the acute inflammatory response.

Chronic Inflammation and Health

Local inflammatory responses are critical in acute infection and injury. However, exaggerated responses and/or chronic inflammation may be detrimental to health. In fact, chronic low-grade inflammation has been implicated in a number of serious medical conditions (Ershler & Keller, 2000; see Figure 54.2). In addition, both IL-6 and CRP have been prospectively associated with increased risk of all-cause of mortality, even among healthy older people (Harris et al., 1999).

Among rheumatoid arthritis patients, IL-6 and its soluble receptor are elevated in synovial fluid and in plasma, and are correlated with disease activity (Madhok, Crilly, Watson, & Capell, 1993). Moreover, among older adults, elevated serum IL-6 is positively associated with markers of physical frailty and inversely related to bone mineral density (Cesari et al., 2004; Giuliani et al., 2001). High levels of inflammatory markers have been prospectively associated with the development of frailty and disability in older adults (Ferrucci et al., 1999). Furthermore, an inverse relation between plasma IL-6 and hippocampal grey matter volume and cognitive performance has been found among healthy individuals (Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008).

Elevated markers of inflammation may increase risk of certain cancers (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006). In experimental and clinical studies, inflammation in and around the tumor appears to promote cancer development and progression (Balkwill, Charles, & Mantovani, 2005). In humans, elevated inflammatory markers have also been associated with poorer prognosis and more severe cancer-related symptoms such as persistent fatigue (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006; Salgado et al., 2003).

Notably, IL-6 is a prospective risk factor for type 2 diabetes (Pradhan, Manson, Rifai, Buring, & Ridker, 2001). Inflammation is also related to atherosclerotic processes and hypertension, which in turn are linked to the development of cardiovascular disorders (Amar et al., 2006; Sesso et al., 2003).

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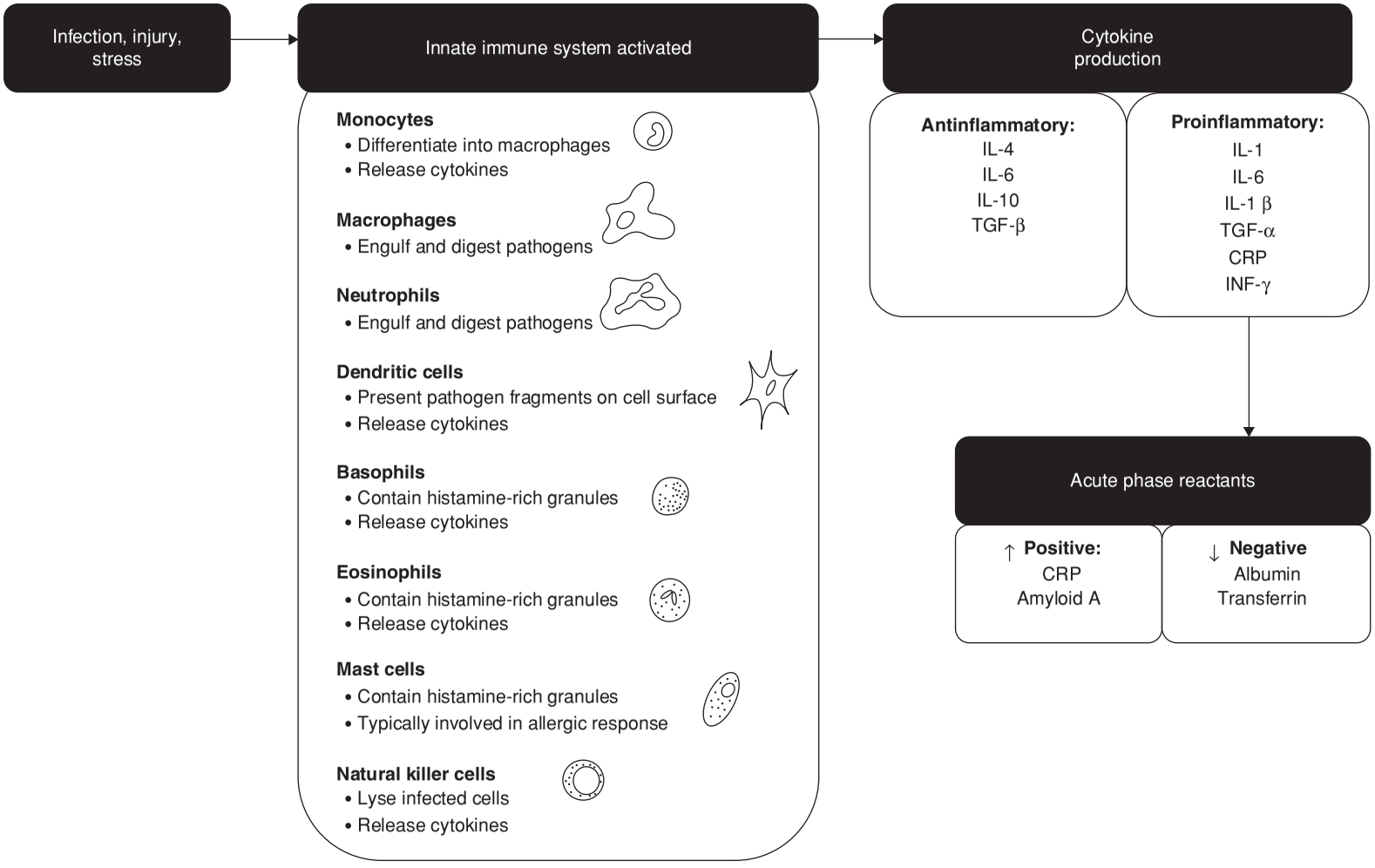

Fig. 54.1 Acute Inflammation: Innate Immune System The innate immune response is the body's immediate, nonspecific reaction to infection, injury, or stress. As opposed to the adaptive immune response, which relies on antibodies, the innate immune response relies on cytokines. Cytokines are signaling molecules which can act in an endocrine, paracrine, or autocrine manner, recruiting other immune cells to the site.

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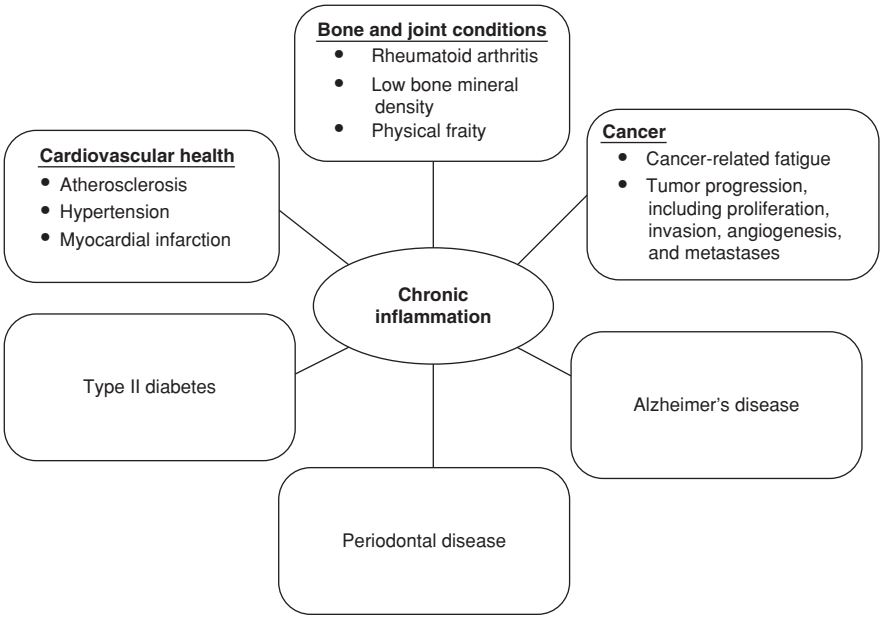

Fig. 54.2 Chronic Inflammation and Health Chronic inflammation is associated with a number of health conditions.

Indeed, plasma levels of IL-6 and CRP have been associated with an increased risk of myocardial infarction, even among apparently healthy individuals (Ridker, Rifai, Stampfer, & Hennekens, 2000; Ridker, 2000). Circulating markers of inflammation also predict a worse prognosis following an acute coronary episode (Lindmark, Diderholm, Wallentin, & Siegbahn, 2001). Moreover, individuals presenting high levels of CRP were at increased risk of developing transient myocardial ischemia during a laboratory mental stressor, a condition associated with increased risk of later, clinically relevant cardiac events (Shah et al., 2006).

Acute Stress and Inflammation

Acute stress elicits peripheral production of proinflammatory cytokines. In animal models, a range of stressors including physical restraint, foot shock, and open field exposure, provoke elevations in circulating markers of inflammation, with the magnitude of the change proportional to the intensity of the stressor (LeMay, Vander, & Kluger, 1990; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993). For example, the increase in circulating IL-6 was proportional to the number of foot shocks administered to the rat (Zhou et al., 1993). Furthermore, this inflammatory response to stress can be conditioned. After pairing the foot shocks with an auditory tone for several trials, the conditioned stimulus (i.e., the auditory tone) acquired the ability to elicit an inflammatory response even in the absence of shock (Johnson et al., 2002; Zhou et al., 1993).

In humans, standardized laboratory stressors lead to increases in inflammation (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004). For example, the Trier Social Stress Test (TSST), a laboratory stressor involving mental arithmetic and a public-speaking task, elicited elevations in plasma IL-6 (Pace et al., 2006). Similarly, exposure to an experimental stressor comprising a computerized color-word interference (i.e., Stroop) task and a mirror tracing task led to an increase in IL-1β gene expression in mononuclear cells (Brydon et al., 2005). A meta-analysis of human studies on the impact of acute stress on circulating markers of inflammation suggests that elevations in plasma levels of IL-6, IL-1β, and CRP are reliably observed after exposure to a standardized psychological stressor. The increase in biomarkers of inflammation appears to be greater 30 to 120 minutes post-stress compared to immediately after the stress task (Steptoe, Hamer, & Chida, 2007). In fact, elevations in circulating markers of inflammation were observed up to 24 hours following the discussion of a marital disagreement in a well-controlled environment (Kiecolt-Glaser et al., 2005). Some null effects observed in the literature may be explained by the fact the blood samples were taken too close to the occurrence of the stressor (e.g. Heesen et al., 2002; Lutgendorf, Logan, Costanzo, & Lubaroff, 2004).

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Short-term naturalistic stressors also appear to promote systemic inflammation. Psychiatry residents who gave an oral presentation before the members of their department exhibited an increase in IL-1β and sICAM, a chemokine whose presence suggest an inflammatory state, as compared to control days when they listened to colleagues giving presentations (Heinz et al., 2003). Similarly, among community-dwelling adults, the frequency of daily hassles in the past month was positively associated with elevated plasma levels of sICAM-1, and the frequency of positive events over the last month was negatively associated with higher IL-6 plasma levels (Jain, Mills, von Kanel, Hong, & Dimsdale, 2007). Self-reported perceived stress has also been cross-sectionally associated with plasma CRP levels (McDade, Hawkley, & Cacioppo, 2006). Low socioeconomic status, a condition often associated with multiple stressors, has been related to greater plasma levels of IL-6, TNF-α, and CRP, compared to higher socioeconomic status (Koster et al., 2006).

Repeated exposure to a standardized stressor does not lead to the habituation of the inflammatory response. Participants who participated in the TSST once a week for three weeks demonstrated reduced cortisol and systolic blood pressure reactivity during the second and third exposure to the stressor. However, the inflammatory responses remained the same across the three experimental sessions (von Kanel, Kudielka, Preckel, Hanebuth, & Fischer, 2005). If such lack of habituation also occurs in naturalistic settings, inflammatory responses to relatively minor but recurrent stress in daily life may contribute to increased low-grade inflammation. Importantly, stress-induced elevations in circulating inflammatory markers have been prospectively associated with the development of subclinical indicators of cardiovascular diseases (Brydon & Steptoe, 2005; Ellins et al., 2008).

In the context of autoimmune and inflammatory diseases, stress-induced increases in inflammation may exacerbate disease activity. Individuals suffering from gingivitis, a chronic inflammation of the oral gingival connective tissue, were randomly exposed to either a public-speaking task or a nonstressful control task. The stress task induced increases in IL-8 production in gingival crevicular fluid, suggesting a mechanism by which stress may promote disease progression (Weik, Herforth, Kolb-Bachofen, & Deinzer, 2008). Among women with rheumatoid arthritis, chronic interpersonal stress was associated with greater LPS-stimulated IL-6 production by peripheral blood mononuclear cells. This increase in IL-6 production was in turn related to greater self-reported fatigue (Davis et al., 2008). Dysregulated inflammatory responses may therefore be detrimental in the context of autoimmune and inflammatory diseases.

Chronic Stress and Inflammation

Chronic stress may promote a state of chronic low-grade inflammation. Family dementia caregiving is one of the best human models of chronic stress. Caregivers must deal daily with the changes in cognitive functioning (e.g., memory loss, confusion), behaviors (e.g., agitation, aggression), and personality (e.g. apathy, inappropriate emotion) of their loved one. Caregivers have an increased risk for anxiety and depressive disorders, a greater frequency of infectious illnesses, poorer responses to vaccines, delayed wound healing, and even an increased risk of death, compared to noncaregiving controls (Gouin, Hantsoo, & Kiecolt-Glaser, 2008).

The chronic stress associated with caregiving has been related to heightened inflammation. Older women caring for a spouse with dementia exhibited higher plasma IL-6 levels compared to older women undergoing the time-limited stress of housing relocation, as well as women who were not experiencing significant life changes (Lutgendorf et al., 1999). These results were replicated in a larger study in which 116 caregivers exhibited higher plasma levels of IL-6 compared to 54 demographically similar noncaregiving controls (von Kanel et al., 2006). Chronic stress also appears to exacerbate the natural age-related increases in IL-6. In a longitudinal study, 119 caregivers exhibited on average a four-fold greater increase in IL-6 over a 6-year period, compared to 106 demographically-similar noncaregiving controls (Kiecolt-Glaser et al., 2003). This amplified age-related increase in IL-6 was not trivial. Based on the results of epidemiological studies, older adults with an IL-6 serum concentration greater than 3.19 pg/ml had a 2-fold greater risk of death. In the Kiecolt-Glaser et al. study (2003), caregivers reached this threshold on average around the age of 75, while noncaregivers were expected to cross that threshold after the age of 90.

The higher frequency of infectious illnesses, poorer responses to vaccine, and delayed wound healing in combination with chronic stress may contribute to greater production of proinflammatory cytokines among caregivers. The subsequent chronic low-grade inflammation is a physiological mechanism that might explain the association between the chronic stress of caregiving and the

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development and progression of age-related diseases, and even death (Black, 2006).

Depression, Mood, and Inflammation

Clinical depression and subsyndromal depressive symptoms have been related to elevated circulating markers of inflammation. Several lines of evidence support the association between depression and inflammation.

Pharmacologically-induced Inflammation is Associated with Depression

In rodents, systemic or central administration of proinflammatory cytokines, IL-1β in particular, induces a sickness behavior syndrome resembling human depression. Behavioral changes following proinflammatory cytokine administration include fever, anorexia, weight loss, psychomotor retardation, sleep disturbances, impaired cognitive abilities, and anhedonia. The fact that these symptoms disappear when the administration of cytokine is interrupted, or with the administration of cytokine antagonists or anti-inflammatory compounds, supports the role of cytokines in causing these depression-like symptoms (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008).

In humans, proinflammatory cytokines are administered therapeutically to treat certain cancers and infectious diseases such as hepatitis C. Patients undergoing IL-2 or interferon (IFN)-α treatment exhibit cognitive disturbances and neurovegetative symptoms such as loss of appetite, fatigue, or altered sleep in the first week of treatment. A few weeks later, sadness and loss of interest are experienced by 40% of the patients receiving cytokine treatment (Capuron, Gumnick et al., 2002). A notable proportion of those patients developed sufficiently severe depressive symptoms to require psychiatric treatment (Dieperink, Ho, Thuras, & Willenbring, 2003). In addition, IFN-α treatment causes increases in circulating IL-6 and TNF-α, and provokes HPA axis alterations, as well as dysregulation of serotonin metabolism (Capuron & Miller, 2004).

Vaccinations can also lead to transient mood disturbances that may be related to inflammatory responses to the immune challenge. Individuals who were vaccinated reported an increase in negative affect and a decrease in positive mood that was correlated with the elevation in serum IL-6 levels following the immune challenge (Wright, Strike, Brydon, & Steptoe, 2005). Similarly, injection of a *salmonella abortus equi* endotoxin led to a 50- to 100-fold increase in plasma IL-6 and TNF-α concentration within 4 hours, but no such increase was observed following administration of the placebo substance. Significant elevations in anxiety and depressed mood were observed in the endotoxin group but not the placebo group (Reichenberg et al., 2001).

Depression Treatment Leads to Reduction in Inflammation

Successful pharmacological treatment of depression reduces circulating markers of inflammation, providing further evidence of an association between depression and inflammation. Antidepressant medication has been associated with reduction in plasma IL-6, TNF-α, and CRP (Lanquillon, Krieg, Bening-Abu-Shach, & Vedder, 2000; Sluzewska et al., 1995). A complementary increase in anti-inflammatory cytokines is also observed in depressed patients responding to antidepressant medication (Leonard, 2001). Furthermore, the depressive symptoms elicited by IFN-α therapy can be prevented or attenuated by antidepressant treatment (Hauser et al., 2002; Musselman et al., 2001). Conversely, some anti-inflammatory medication can have antidepressant effects. Patients with psoriasis who received etanercept, a TNF-α antagonist, exhibited reductions in depressive symptoms independent of improvement in disease activity. Such improvement in depressive symptoms was not observed among patients who received a placebo medication (Tyring et al., 2006).

Behavioral interventions targeting stress and depression may also impact inflammatory activity. A mindfulness-based stress reduction intervention with cancer patients led to reduction in proinflammatory cytokines as well as a complementary increase in anti-inflammatory cytokines (Carlson, Speca, Patel, & Goodey, 2003). Similarly, during a meditation intervention, individuals who engaged in meditation practices more frequently had a lower IL-6 response to a laboratory stressor, the TSST (Pace et al., 2009). Furthermore, a cognitive-behavioral intervention targeting stress and depression among cardiac patients led to a reduction in plasma proinflammatory cytokines (Doering, Cross, Vredevoe, Martinez-Maza, & Cowan, 2007).

Association Between Depression and Inflammation in Epidemiological and Clinical Studies

Syndromal depressive disorders as well as depressive symptoms have been associated with increased systemic inflammation. Several studies have noted

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an elevation of 40 to 50% in the serum concentrations of IL-6 and CRP among clinically depressed patients relative to control participants who had no psychiatric history (Ford & Erlinger, 2004; Irwin, 2002; Maes et al., 1997; Miller, Stetler, Carney, Freedland, & Banks, 2002; Pike & Irwin, 2006). In epidemiological studies, individuals presenting subsyndromal depressive symptoms also exhibited higher serum concentrations of CRP, IL-6, TNF-α and IL-1β compared to individuals reporting no or low levels of depressive symptoms (Dentino et al., 1999; Kop et al., 2002; Penninx et al., 2003; Suarez, Krishnan, & Lewis, 2003; Thomas et al., 2005). A meta-analysis confirmed the positive association between depressive symptoms, clinical depression and elevations in plasma IL-1β, IL-6, and CRP (Howren, Lamkin, & Suls, 2009).

Chronic Diseases, Inflammation, and Depression

Some authors argue that the high prevalence of depression seen in cardiovascular, cancer, diabetes, and rheumatoid arthritis patients may in part be due to the state of chronic inflammation found in these medical conditions (Raison, Capuron, & Miller, 2006). Infectious and inflammatory diseases have also been associated with behavioral alterations resembling depression such as malaise, lethargy, anorexia, hypersomnia, and anhedonia (Larson & Dunn, 2001). Indeed, high levels of proinflammatory cytokines have been associated with clinical depression among patients with diverse diseases (Bonaccorso et al., 2002).

Bidirectional Relationships Between Mood and Inflammation

Even transient mood disturbances may impact peripheral inflammatory activity. Academic examination-induced anxiety has been associated with greater production of serum TNF-α, IL-6, and IFN-γ among medical students (Maes et al., 1998). Similarly, increased anxiety in response to a laboratory stressor was associated with a higher level of IL-1β gene expression, suggesting that mood disturbance following exposure to a stressor contributes to changes in systemic inflammation (Brydon et al., 2005). Moreover, state depressive symptoms in the past week that represented a deviation from trait or typical depressive symptoms over the past 6 months were associated with elevated plasma IL-6 levels (Rohleder & Miller, 2007). Collectively, these data suggests a bidirectional relationship between mood and inflammation.

Other Negative Emotions and Inflammation

Other negative emotions have also been associated with increased inflammation. Individuals with post-traumatic stress disorder (PTSD) had greater LPS-stimulated IL-6 production, compared to individuals without such anxiety disorder (Rohleder, Loksimovic, Wolf, & Kirschbaum, 2004). Furthermore, elevated morning plasma IL-6 levels predicted the development of PTSD symptoms among children involved in motor vehicle accidents (Pervanidou et al., 2007). Anger and hostility have also been associated with increased inflammation (Graham et al., 2006; Marsland, Prather, Petersen, Cohen, & Manuck, 2008; Suarez, Boyle, Lewis, Hall, & Young, 2006). Depression and hostility appear to interact in predicting basal levels of inflammation. Individuals with high levels of both depression and hostility have higher levels of IL-6 and CRP, compared to individuals with high levels of hostility but lower levels of depressive symptoms (Stewart, Janicki-Deverts, Muldoon, & Kamarck, 2008). The self-conscious emotion of shame has been related to elevated biomarkers of inflammation. Participants assigned to write about a traumatic experience in which they blame themselves had increased TNF-α soluble receptor activity, compared to participants who wrote about neutral experiences (Dickerson, Kemeny, Aziz, Kim, & Fahey, 2004). Similarly, greater self-reported shame was also associated with elevated circulating markers of inflammation among young women (Rohleder, Chen, Wolf, & Miller, 2008). Figure 54.3 summarizes the relationship between depression and inflammation.

Cross-sensitization: Stress, Depression, and Inflammation

Stress and depression can also sensitize the immune system to the action of other stressors. Rats exposed to stressors such as inescapable tail shocks or social disruption exhibited amplified inflammatory and sickness behavior responses to the administration of a bacterial endotoxin, compared to rats that were not exposed to stressors (Gibb, Hayley, Gandhi, Poulter, & Anisman, 2008; Johnson et al., 2002). In humans, stress can also amplify inflammatory response to additional stressors. Healthy volunteers who both received a typhoid vaccination and were exposed to the psychological stressor exhibited greater increases in serum IL-6, compared to participants who were not randomized to both the active vaccine and the psychological stressor (Brydon et al., 2009).

Depression can also amplify inflammatory responses to psychological stressors. Men with a

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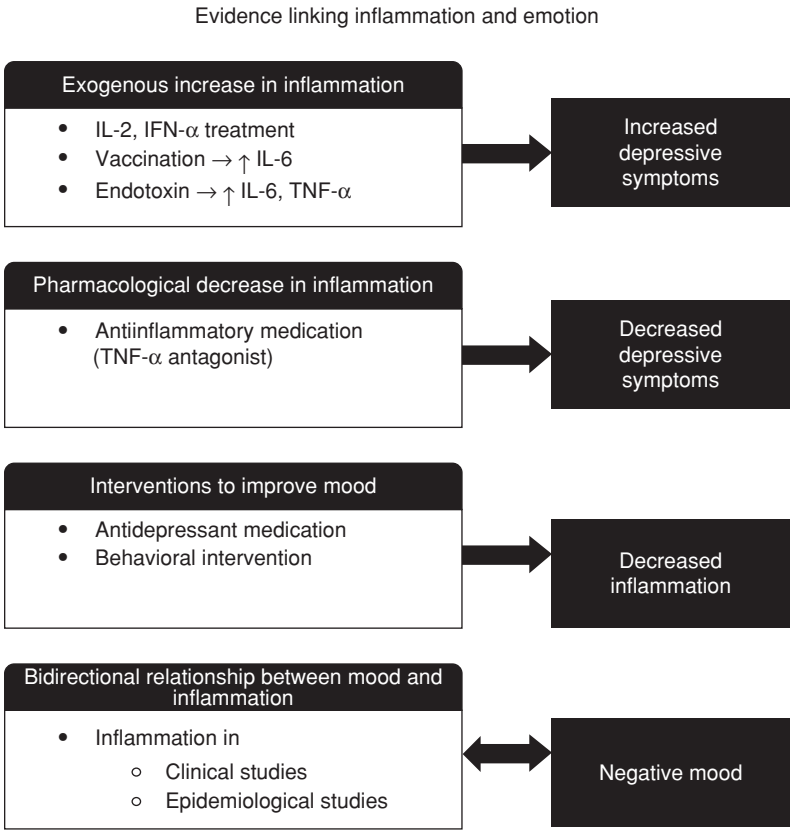

Fig. 54.3 Negative emotions and inflammation experimental and correlational research in animals and humans demonstrates bidirectional relationships between inflammation and mood.

diagnosis of major depression had significantly greater mononuclear cell NF-κB activation, a gene involved in the production of inflammatory proteins, and greater increases in plasma IL-6 following exposure to the TSST, compared to participants with no history of affective disorder (Pace et al., 2006). Depression may also exacerbate CRP response to psychological stress. Individuals without depression had a sharper increase in CRP following exposure to a laboratory stressor, but their CRP levels declined to baseline during the recovery. In contrast, depressed individuals had a smaller CRP increase following exposure to the stressor; however, CRP levels kept rising during the recovery to the levels that the controls reached immediately after the stressor (Miller, Rohleder, Stetler, & Kirschbaum, 2005). Furthermore, depressed individuals with a history of childhood maltreatment had greater basal CRP plasma levels, compared to depressed individuals who did not experience childhood adversities (Danese, Pariante, Caspi, Taylor, & Poulton, 2007).

In addition, depression may sensitize the immune response to other nonpsychological stressors. Older adults reporting depressive symptoms had an amplified IL-6 response up to two weeks after influenza immunization, compared to individuals reporting no depressive symptoms (Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003). This result is especially noteworthy because even relatively low levels of depressive symptoms can amplify the inflammatory response to the influenza vaccine (Glaser et al., 2003).

Social Relationships and Inflammation

There is a robust relationship between social relationships and immunity (Graham, Christian, & Kiecolt-Glaser, 2007). Social support and positive social relationships have been associated with lower circulating markers of inflammation among cancer patients and healthy volunteers (Costanzo et al., 2005; Friedman et al., 2005; Lutgendorf, Anderson, Sorosky, Buller, & Lubaroff, 2000; Lutgendorf et al., 2002). Conversely, low social support has been

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related to higher plasma CRP and greater LPS-stimulated IL-8 production (Coussons-Read, Okun, & Nettles, 2007; Marsland, Sathanoori, Muldoon, & Manuck, 2007). In an epidemiological study, social integration was inversely related to plasma CRP and IL-6 in men (Loucks et al., 2006). In a similar vein, socially isolated individuals presented a shift from anti- to proinflammatory gene expression (Cole et al., 2007). Furthermore, greater religious participation has also been related to lower levels of systemic inflammation (Koenig et al., 1997; Lutgendorf, Russell, Ullrich, Harris, & Wallace, 2004).

Negative social interactions have been associated with elevations in circulating markers of inflammation. Couples who exhibited more negative and hostile behaviors during the discussion of marital disagreement had greater increases in IL-6 and TNF-α, compared to less hostile couples (Kiecolt-Glaser et al., 2005). This effect was even more pronounced among individuals with higher levels of attachment avoidance (Gouin et al., in press). Moreover, healthy young women reporting chronic interpersonal difficulties exhibited a greater increase in messenger ribonucleic acid (mRNA) for the proinflammatory transcription factor NF-κB, and greater LPS-stimulated IL-6 production over the next 6 months (Miller, Rohleder, & Cole, 2009). Furthermore, in a 32-year prospective study, childhood maltreatment, a major interpersonal stressor, was associated with increased plasma CRP levels in adulthood (Danese et al., 2008).

Behavioral Pathways Linking Negative Emotions and Inflammation

Changes in health behaviors may partially mediate the relationship between stress, depression, and inflammation. Stress and depression often elicit the adoption of detrimental health behaviors, including smoking and alcohol use, reduction in physical activity, poor diet choices, and less sleep (Steptoe, Wardle, Pollard, Canaan, & Davies, 1996; Vitaliano, Scanlan, Zhang, Savage, & Hirsch, 2002). Several of these negative health behaviors have been associated with elevated biomarkers of systemic inflammation.

In population-based studies, smoking and greater alcohol intake were associated with greater plasma CRP levels (Hamer & Chida, 2009; Nazmi, Oliveira, & Victora, 2008). Acute exercise triggers transient increases in plasma IL-6 and TNF-α that are important for muscle repair, cell turnover, and regulation of lipids (Petersen & Pedersen, 2005). However, lack of regular physical activity is associated with higher basal levels of circulating inflammatory markers (e.g., Elosua et al., 2005; Ford, 2002).

Diets high in saturated fat may fuel chronic low-grade inflammation. A high-fat meal, but not a high-carbohydrate meal, was associated with subsequent increases in plasma IL-6 (Nappo et al., 2002). In epidemiological studies, high levels of omega-3 (*n*-3) polyunsaturated fatty acids have been associated with lower circulating makers of inflammation (Ferrucci et al., 2006). Lower levels of *n*-3 appear to interact with stress and depression to promote increased inflammatory responses. Students with a higher *n*-6: *n*-3 ratio had greater inflammatory reactivity to academic examination stress, compared to students with lower *n*-6: *n*-3 ratio (Maes, Christophe, Bosmans, Lin, & Neels, 2000). Similarly, among older adults, depression interacted with the *n*-6: *n*-3 ratio to predict higher basal levels of circulating markers of inflammation (Kiecolt-Glaser et al., 2007).

Obesity, a condition associated with poor eating habits and low exercise levels, is also associated with increased plasma levels of inflammatory mediators (Vachharajani & Granger, 2009). Systemic inflammation was once thought to be primarily the result of production of IL-6 by immune cells, but recent data reveal that more than one-third of the circulating IL-6 may originate from adipocytes (Mohamed-Ali, Pinkney, & Coppack, 1998). Furthermore, abdominal fat can amplify cortisol and inflammatory responses to psychological stress (Brydon et al., 2008; Epel et al., 2000).

Finally, both objectively measured and self-reported sleep disturbances have been associated with increases in circulating markers of inflammation (Mills et al., 2007). In a large epidemiological study, greater self-reported sleep disturbances were associated with greater CRP plasma levels in men (Liukkonen et al., 2007). Among older women, objectively measured sleep efficiency was inversely related with plasma IL-6 levels (Friedman et al., 2005). Figure 54.4 summarizes the health behaviors that may be part of a behavioral mechanism linking stress and inflammation.

Physiological Pathways Linking Negative Emotions and Inflammation

Regulation of Monoamines

Cytokines and their receptors have been found in the hypothalamus, the hippocampus, the prefrontal cortex, and the brain stem (Miller, 1998). The action of cytokines may be mediated by their impact on the serotonergic and other monoamine systems.

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Fig. 54.4 Health behaviors associated with inflammation.

In rats, intraventricular injections of IFN-α reduced the level of 5-HT in the brain (Kamata, Higuchi, Yoshimoto, Yoshida, & Shimizu, 2000). Proinflammatory cytokines can decrease the availability of tryptophan (TRP) in the brain by activating the enzyme indoleamine-2,3 dioxygenase, which provokes a switch from the synthesis of TRP to the synthesis of kynurenine and quinolinic acid, thereby reducing the production of 5-HT (Schiepers, Wichers, & Maes, 2005). Decreased CSF levels of TRP have been positively correlated with the development of depressive symptoms among cancer patients treated with IFN-α (Capuron, Ravaud, et al., 2002). In addition, several proinflammatory cytokines (TNF-α, IL-1β, IFN-γ) reduced the activity of the 5-HT transporter, which may result in a decrease in extracellular levels of 5-HT (Bonaccorso et al., 2002). Cytokines may also influence the synthesis and reuptake of dopamine and norepinephrine (Kitagami et al., 2003; Moron et al., 2003). Furthermore, inflammation may reduce neural plasticity. Pharmacologically induced inflammation via LPS injection was associated with cognitive impairment, decreased hippocampal expression of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase-B, as well as reduced hippocampal neurogenesis in rats (Wu et al., 2007).

Glucocorticoid Resistance

Cortisol plays an important role in regulating inflammatory responses. However, chronic low-grade levels of inflammation may excessively prolong the activation of the HPA axis. Several proinflammatory cytokines can stimulate the production of corticotropin-releasing hormone (Besedovsky et al., 1991). Usually, cortisol, the end product of HPA-axis activation, has anti-inflammatory properties. However, in the case of chronic exposure to cortisol, a down-regulation of glucocorticoid receptors is observed (Miller, Pariante, & Pearce, 1999). This leads to glucocorticoid resistance, whereby immune cells are less responsive to the anti-inflammatory properties of glucocorticoids. This process can then promote chronic elevations in circulating markers of inflammation. In fact, the chronic stress of caregiving for a child with cancer has been associated with diminished inhibition of LPS-stimulated IL-6 production following administration of a synthetic glucocorticoid (Miller, Cohen, & Ritchey, 2002).

Molecular Mechanism Linking Stress and Inflammation

A direct molecular mechanism linking stress and inflammation has been detailed by Bierhaus and collaborators (Bierhaus et al., 2003). Exposure to the TSST led to an increase in the nuclear factor NF-κB from peripheral blood monocyte cells within 10 minutes among healthy volunteers. NF-κB is a transcription factor that influences the expression of the genes of several inflammatory mediators (Barnes & Karin, 1997). In humans, activation of NF-κB was correlated with stress-induced catecholamine and cortisol secretion. Animal studies specified that binding of norepinephrine, but not epinephrine, led to a downstream signaling cascade that resulted in the activation and translocation of NF-κB in the nucleus of the cells (Bierhaus et al., 2003). Therefore, stress-induced increases in norepinephrine might lead to the activation of NF-κB and, subsequently, to increased gene expression of inflammatory proteins. Individuals caring for a relative with a brain tumor exhibited higher plasma levels of CRP, greater expression of the NF-κB-related genes, as well as decreased expression of glucocorticoid receptor-related genes, suggesting that chronic stress also activates the NF-κB pathway (Miller et al., 2008). Figure 54.5 depicts different physiological pathways linking stress and inflammation.

Conclusion

Inflammation is a vital process involved in infection clearance and wound healing. However, converging evidence suggests that stress and negative emotions can promote a state of chronic low-grade inflammation, which has been associated with detrimental health outcomes. Although some studies suggest that increased inflammation may reflect simply the presence of risk factors or represent a marker of disease activity, other evidence suggests that inflammation may have a causal pathophysiological role. For social neuroscientists, inflammation may thus become a key physiological mediator of the impact of stress and negative emotions on health.

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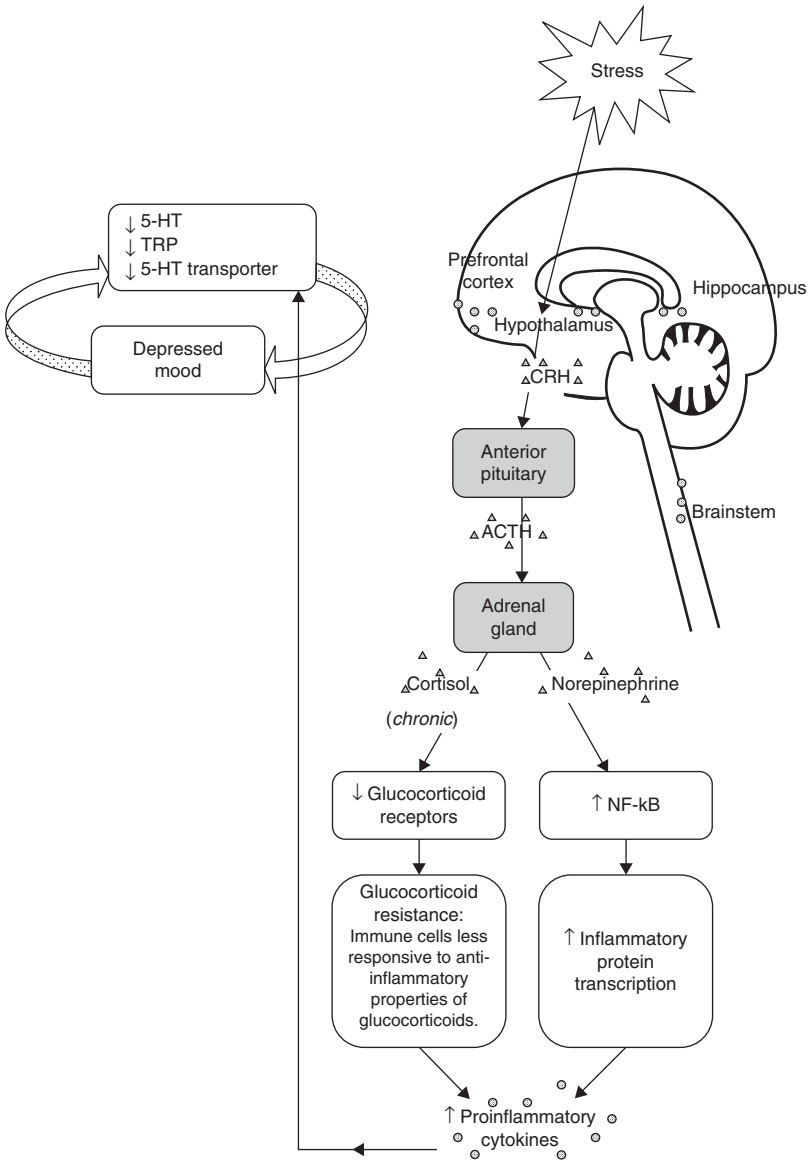

Fig. 54.5 Physiological pathways. A pathway linking stress, immune function, and mood. Cytokine receptors (•) are found in the prefrontal cortex, hippocampus, hypothalamus, and brainstem. Stress acts on the hypothalamus, inducing release of cortisol from the adrenal cortex, and norepinephrine from the adrenal medulla. With chronic stress, excess cortisol is released, resulting in downregulation of glucocorticoid receptros. This makes immune cells responsive to glucocorticoids' antiinflammatory properties, resulting in increased levels of proinflammatory cytokines. Norepinephrine release activates NF-κB, which increases gene production of inflammatory proteins. Proinflammatory cytokines affect serotonergic (5-HT) function, which may, in turn, impact mood.

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