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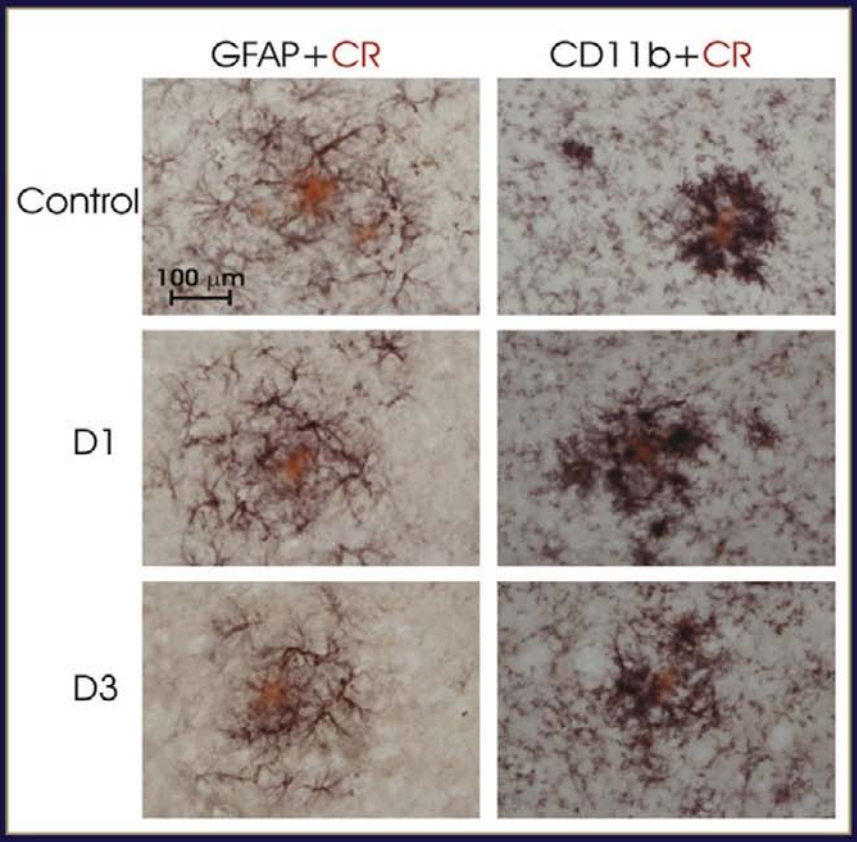

Edited by
Rossen Donev

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PREFACE

Inflammation is a complex biological response to harmful stimuli such as cellular damage and pathogens. In general, it is a protective effort of the organism to remove the harmful stimuli. However, when it occurs chronically, inflammation can lead to a number of adverse effects. Inflammatory responses in the brain have been recognized for years as critical in neurodegeneration and behavior in some neurological disorders (e.g., multiple sclerosis, Alzheimer's disease). However, in recent years, researchers discovered that certain inflammatory responses are involved in correct development of the brain and in neurogenesis as well as in the protection of our brain from neurodegeneration. The presence or absence of some of the inflammatory responses in the brain often can be a result of a particular combination of polymorphisms in groups of genes controlling signaling pathways and/or protein activation cascades such as complement system. These findings suggest the important role of inflammation in neurodevelopmental disorders which has been largely overlooked so far. Now it becomes more obvious that inflammation plays a dual role in our brain and therefore further in-depth studies on the role of inflammation in neuropsychiatric disorders are urgently required. These will allow the correct design of drugs targeting the adverse effect from inflammation while maintaining the benefits for the brain.

The goal of this thematic volume of the *Advances in Protein Chemistry and Structural Biology* is to provide a comprehensive view of the mechanisms triggering inflammatory responses in the brain and leading to different neuropsychiatric disorders as well as some novel approaches for their treatment. This thematic volume provides a rationale for future studies on the relationship between inflammation and neuropsychiatric disorders with intent to inspiring the development of new agents for a more efficient management and prevention.

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CHAPTER ONE

Inflammation in Anxiety

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Abstract

The idea of the existence of an interaction between the immune system and the central nervous system (CNS) has prompted extensive research interest into the subject of "Psychoneuroimmunology" taking the field to an interesting level where new hypotheses are being increasingly tested. Specifically, exactly how the cross talk of pathways and mechanisms enable immune system to influence our brain and behavior is a question of immense significance. Of particular relevance to this topic is the role of cytokines in regulating functions within the CNS that ultimately modulate behavior. Interestingly, psychological stress is reported to modulate cytokine production, suggesting potential relevance of this mediator to mental health. In fact, cytokine signaling in the brain is known to regulate important brain functions including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, as well as the neural circuitry of mood. It is rather obvious to expect an aberrant behavioral outcome as a result of a dysregulation in cytokine signaling which might lead to occurrence of depression, anxiety, and cognitive dysfunction. Thus, understanding the mechanisms by which the immune system influences behavior would reveal targets for potential therapeutic development as well as strategies for the prevention of neuropsychiatric diseases. To date, the presence of inflammatory responses and the crucial role of cytokines in depression have received most attention. However, considering a big socioeconomic impact due to an alarming increase in anxiety disorder patients, there is an urgent research need for a better understanding of the role of cytokines in anxiety. In this review, we discuss recent research on the role of neuroimmunology in anxiety. At the end, we offer an "oxidative stress theory," which we propose works perhaps as a "sensor of distress," the imbalance of which leads to neuroinflammation and causes anxiety disorders. *Much research is needed to extensively test this theory keeping an open mind*!

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ABBREVIATIONS

ARB angiotensin AT1 receptor blocker
BBB blood–brain barrier
BDNF brain-derived neurotrophic factor
BSO buthionine sulfoximine
CaMK Ca^{2+}/calmodulin protein kinase
CNS central nervous system
COX cyclooxygenase
CREB cAMP response element-binding
CRP C-reactive protein
GABA gamma amino butyric acid
GLO glyoxalase
GSR glutathione reductase
HPA hypothalamic–pituitary–adrenal
IFN interferon
IL interleukin
LC locus coeruleus
MG methylglyoxal
NFκB nuclear factor kappaB
RNS reactive nitrogen species
ROS reactive oxygen species
Th1 type 1 helper
Th2 type 2 helper
TNF tumor necrosis factor
X + XO xanthine + xanthine oxidase

1. INTRODUCTION

Psychological stress is a key determinant of health and disease and reported to lead to a variety of diseases whose onset and course are now considered to be influenced by the immune system. Identified by the Egyptians, pursued by the Romans, and centuries later defined by modern researchers, as a natural immune response against stress, inflammation has become a topic of extensive research. Inflammation is considered as a key component of host defense response to injury, which is associated with adherence, and invasion of leukocytes into injured or infected tissues, and is a vital part of the immune system. Inflammation is generally considered as protective when its mechanism of action is to contain injury or infection locally. However, inflammation becomes harmful when it gets excessive (overexpression or overactivity of mediators) over time. Therefore, inflammation may have beneficial as well as detrimental actions, particularly during repair and

recovery processes. For example, chronic inflammation becomes pathological upon continued active inflammatory response and extended tissue destruction. Many of the immune cells including macrophages, neutrophils, and eosinophils are involved directly or by producing inflammatory mediators in the pathology of chronic inflammation. Immune system comprises a sophisticated set of mechanisms coordinated by the interaction of a variety of specific mediators called cytokines, prostaglandins, chemokines, and others that generate nonspecific physiological responses including sickness behavior and hypothalamic–pituitary–adrenal (HPA) axis activation (Allan & Rothwell, 2003). Just as the nervous and endocrine systems convey information to the immune system via neurotransmitters and hormones, the immune system transmits information to the nervous and endocrine systems via specific mediators called cytokines and chemokines (Leonard & Myint, 2009). Cytokines are soluble mediators released both at the periphery (e.g., monocytes and macrophages) and in the brain (e.g., microglia, astrocytes, oligodendroglia, and neurons) and are associated with inflammation, immune activation, cell differentiation, and cell death (Allan & Rothwell, 2003). Cytokine production is controlled by type 1 helper (Th1) and type 2 helper (Th2) cells. Th1 cells mediate a proinflammatory cellular immune response, while Th2 cells enhance humoral immune reactions. Proinflammatory cytokines, including interleukin (IL)-1, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, enhance the immune response to eliminate pathogens, while anti-inflammatory cytokines, including IL-4, IL-10, and IL-13, dampen the immune response by reducing the synthesis of proinflammatory cytokines (Kronfol & Remick, 2000). The balance between Th1 and Th2 therefore is important in limiting the inflammatory response (Dantzer et al., 2008), and a delicate balance of proinflammatory and anti-inflammatory cytokines is critical (Loftis, Huckans, & Morasco, 2010). In addition to exogenous immune influences, brain's own endogenous responses also impact the healthy and diseased central nervous system (CNS) and primarily comprise myeloid cells known as microglia. Microglia are macrophages that constitute the first line of innate immune defense in the brain. Usually deactivated under normal physiological conditions, microglia switch to an activated form in response to tissue damage or invasion of a pathogen and promote an inflammatory response by releasing factors that engender responses analogous to the responses of activated immune cells in the periphery (Glass, Saijo, Winner, Marchetto, & Gage, 2010). These endogenous and

exogenous immune responses in the CNS do not function in isolation, rather display a dynamic interplay among themselves (Rezai-Zadeh, Gate, & Town, 2009).

For a long time, inflammation in the CNS was largely considered as bleed-over of peripheral immune responses to pathogens (viruses, bacteria, parasites) invading the CNS or an element of some type of CNS autoimmune diseases. It was generally believed that the blood–brain barrier (BBB) prevented access of immune cells to the brain and, as a result, the immune system and the CNS were believed to be relatively independent of each other. This view of inflammation is now drastically changed. It has become quite clear that BBB permeability is modulated, and trafficking of peripheral macrophages and leukocytes into the brain parenchyma occurs in a tightly regulated manner and helps promote brain homeostasis and prevent neuronal death (Ransohoff & Perry, 2009; Rezai-Zadeh et al., 2009). Thus, the CNS despite the selectivity imposed by the BBB actually responds to peripheral inflammatory stimuli and elicits a local inflammatory response called neuroinflammation. Specific routes for the movement of peripheral cytokine signals to the brain are now known (Capuron & Miller, 2011). Moreover, it also is now well established that cytokines modulate neuronal activity in specific brain regions such as the amygdala, hippocampus, hypothalamus, and the cerebral cortex (Besedovsky & del Rey, 1996; Elenkov, Wilder, Chrousos, & Vizi, 2000). It is interesting to note that these brain regions have been previously implicated in regulation of stress response (Davis, 2002). It is quite apparent that psychological stress, infection, or inflammation within the brain or the periphery can modulate cytokine expression within the CNS (Lucas, Rothwell, & Gibson, 2006). Behavioral consequences of these effects include the occurrence of several neuropsychiatric disorders (Capuron & Miller, 2011). Consequently, inflammation is now a well-recognized contributor to acute and chronic CNS disorders. In fact, neuroimmune dysregulation is believed to be responsible for the chronic elements of neurodegenerative diseases. Although it cannot be concluded with utmost certainty that neuroinflammation plays a causal role in neurodegeneration, epidemiological and preclinical data suggest that chronic neuroinflammation triggers neuronal dysfunction during the asymptomatic stage of neurodegenerative diseases including Parkinson's and Alzheimer's diseases. Moreover, evidence from medical studies implicates the immune system in a number of psychiatric disorders with developmental origins, including schizophrenia, anxiety, depression, and cognitive dysfunction. Several excellent reviews have discussed in depth many important aspects of CNS inflammation, with regard

to neurodegeneration and neuropsychiatric ailments (Gebicke-Haerter, 2001; Nguyen, Julien, & Rivest, 2002; Perry, Bolton, Anthony, & Betmouni, 1998). Clearly, the most studied and documented area has been major depression. Ever since the involvement of immune function in depression was first reported (Maes et al., 1990, 1991, 1992a, 1992b), numerous studies examining the role of cytokines in major depression have been reported. However, research data and literature reviews on anxiety and neuroinflammation are particularly lacking. Hou and Baldwin (2012) and Hovatta, Juhila, and Donner (2011) recently presented an excellent review of anxiety–inflammation literature. The purpose of this review is not to revisit the same ground, but to present an overview of the critical features of inflammation and to reveal mechanisms potentially critical to anxiety disorders in particular. Limitations of current approaches and gaps in our knowledge as well as implications of recent discoveries also are discussed. Finally, we will speculate on the role and therapeutic potential of some targets of the inflammatory cascade that may be critical to the understanding of anxiety disorders.

2. CYTOKINES, BRAIN, AND BEHAVIOR

Cytokines are proteins, peptides, or glycoproteins released by cells that serve as cellular signals to regulate immune response to injury and infection. Initially described as immune cell mediators in the periphery, they are also expressed in the CNS and are involved in the modulation of various neurological functions (Viviani, Bartesaghi, Corsini, Galli, & Marinovich, 2004; Viviani & Boraso, 2011; Viviani, Gardoni, & Marinovich, 2007). In the brain, cytokines work as an integrated network by inducing their own synthesis as well as that of other proinflammatory cytokines. Cytokine signals originating in periphery reach the brain through humoral, neural, and cellular pathways (Capuron & Miller, 2011). Cytokines are classified as proinflammatory and anti-inflammatory. The proinflammatory cytokines include IL-1, IL-6, and TNF which promote inflammation, a beneficial effect in early immune responses to infection or injury (Glaser, Rabin, Chesney, Cohen, & Natelson, 1999). The primary purpose of cytokines is to attract immune cells to the site of infection or injury and activating them to respond. Other actions secondary to these include changes in physiology to promote inflammation, like alterations in metabolism and temperature regulation. Anti-inflammatory cytokines such as IL-10 and IL-13 dampen the immune response, causing, for

instance, restoration of cellular function and inhibition of proinflammatory cytokine synthesis. The immune system's inflammatory response can be triggered in a variety of ways, including infection and trauma. Other commonly known inflammatory mediators include complement adhesion molecules, cyclooxygenase (COX) enzymes, and their products. Proinflammatory cytokines, including IL-1, IL-6, and TNF-α, are released not only by activated immune cells during the host response to pathogen invasion or during tissue injury but also upon psychological stress. Cytokines are known to mediate the communication between the immune system and the brain, and seem to coordinate cellular response to immune challenges, and enable behavioral changes needed for recovery. The release of proinflammatory cytokines during an immune response is generally transient and regulated by anti-inflammatory mechanisms. Thus, behavioral effects initiated by the activation of the inflammatory response develop as temporary and controlled reaction of the CNS to immune signals. However, when immune challenge becomes chronic, as that observed in patients with chronic medical illness and/or facing persistent psychological stress, the behavioral effects of cytokines and the resultant inflammatory response may contribute to the development of neuropsychiatric diseases. There is abundant information regarding the pathways and mechanisms via which the immune system potentially influences brain and behavior. Role of proinflammatory cytokines in regulating functions in the CNS is well known. Interestingly, psychological stress has been shown to increase cytokine production. Cytokine signaling in the brain is known to regulate important brain functions including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and mood-regulating neural circuitry. The behavioral outcome of any type of dysregulation of the immune system in the CNS might lead to occurrence of depression, anxiety, cognitive dysfunction, and sleep impairment.

Considering the tremendous attention generated with regard to inflammation as a causal factor for many illnesses including cardiovascular disease, diabetes, and cancer, as well as its role in depression and anxiety disorders, it is imperative to identify specific molecular targets of immune function that may be critical for novel immune-based therapeutics for mental health disorders. Tremendous amount of work has been done with regard to depression. Involvement of cytokines and inflammatory factors in the pathophysiology of depression has been proposed by several groups (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Miller, Maletic, & Raison,

2009; Raison, Capuron, & Miller, 2006). Increased prevalence of comorbidity between depression and chronic inflammatory diseases like rheumatoid arthritis, cancer, infectious diseases, autoimmune, and cardiovascular disease (Evans et al., 2005) lends further support to this proposition. In depressed patients, TNF-α, IL-6, and C-reactive protein (CRP) are reported to be elevated in several studies (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009; Zorrilla et al., 2001), and a convincing role of inflammation in the pathophysiology of depression has been reported by several groups (Capuron & Miller, 2004; Musselman et al., 2001; Raison et al., 2005). In particular, elevated inflammatory markers including proinflammatory cytokines, chemokines, and adhesion molecules have been reported in the blood and cerebrospinal fluid of patients with major depression (Dowlati et al., 2010; Howren et al., 2009; Miller et al., 2009; Zorrilla et al., 2001). Significant correlation has also been described between markers of inflammation and neuropsychiatric symptoms including fatigue and cognitive dysfunction (Bower et al., 2009; Jehn et al., 2006; Lutgendorf et al., 2008; Meyers, Albitar, & Estey, 2005; Musselman et al., 2001). Furthermore, alterations in immune function have been found in patients with major depression. Reports of immune suppression (e.g., reduced natural killer cell activity and reduced lymphocyte proliferation) followed by increased inflammatory activity (e.g., increased circulating levels of inflammatory markers) have been described (Anisman, Ravindran, Griffiths, & Merali, 1999; Irwin & Gillin, 1987; Kronfol & Remick, 1983; Maes et al., 1993; Zorrilla et al., 2001). During an infection, the proinflammatory response that is essential for an active immune defense is normally contained by cortisol and also by parasympathetic activity (Borovikova et al., 2000; Munck & Guyre, 1991). Yet, inadequate containment often leads to septic shock and death, and treatment with cortisol and elevation of parasympathetic activity are two pathways to reduce an excessive inflammatory response (Munck & Guyre, 1991). At the opposite extreme, too much cortisol can compromise immune defenses by suppressing the proinflammatory responses (Munck & Guyre, 1991; Sapolsky, Romero, & Munck, 2000). These two examples of too much or too little activity of certain mediators of allostasis illustrate allostatic overload (McEwen & Wingfield, 2003). Allostatic overload is generally defined as the wear and tear produced by imbalances in allostatic mediators. Some other examples of allostatic overload include conditions like hypertension, atherosclerosis, diabetes, and metabolic syndrome, and

stress-induced remodeling in brain regions which determine learning and memory functions and anxiety (McEwen, 2004; McEwen & Wingfield, 2003). Such changes in brain structure are seen in major depression and Cushing's disease.

3. INFLAMMATION IN ANXIETY DISORDERS

Although depression has received most attention, relevance of inflammation to other neuropsychiatric diseases including anxiety disorders is inevitable considering the impact that cytokines have on neurotransmitter systems and associated circuitry related to anxiety response. However, due to the increased comorbidity between depression and anxiety, it becomes incredibly difficult to separate cause–effect relationship between the two especially when considering the involvement of a third component such as neuroinflammation. It is likely that critical brain–immune system interactions occur that are unique to each condition and regulate the biochemistry within specific brain areas that determine depression and anxiety differently. Some suggest that, since antidepressants have a protective effect on both anxiety and depression, similar neurobiological substrates are affected. A complete overlap of biochemistry within the CNS in the two disorders seems unlikely. While psychological chronic stress, by causing changes in the HPA and the immune system, can elicit anxious and depressive behaviors simultaneously (Leonard & Myint, 2009), the possibility that different circuits are activated and novel signaling cascades are involved is an intriguing possibility. This scenario makes lot of sense when one considers the data suggesting higher levels of IL-6 in people with anxiety, independent of depressive symptoms suggesting an anxiety-specific effect on inflammatory response. Perhaps this is one of the pathways via which anxiety increases the risk for other inflammatory conditions (O'Donovan et al., 2010). Whether anxiety is causal for inflammation or inflammation elicits anxiety response is an intriguing question. Our position on this issue is that perhaps inflammation mediates critical biochemical changes within specific areas of the brain which leads to anxiety phenotype. Some of this biochemistry will be addressed below.

Research in the past several years has shown quite interesting results. Several animal studies suggest a potentially important role of neuroinflammation in anxiety. For example, increased cytokine expression in the periphery was reported to be associated with heightened anxiety-like behavior in mice (Sakic et al., 1994; Schrott & Crnic, 1996). Moreover, mice

overexpressing IL-6 or TNF developed an anxiogenic phenotype (Connor & Leonard, 1998; Fiore et al., 1998). Interestingly, deletion of the gene encoding IFN-γ enhances anxiety-like behavior in rodents (Fiore et al., 1998; Kustova, Sei, Morse, & Basile, 1998; Lesch, 2001). As far as the human studies are concerned, there is considerable amount of data showing that high level of anxiety is associated with impaired cellular immunity (Boscarino, 2004; Godbout & Glaser, 2006; Schneiderman, Ironson, & Siegel, 2005; Zhou et al., 2005), including damage to cellular and humoral immune responses (Arranz, Guayerbas, & De la Fuente, 2007; Koh & Lee, 2004; Zhou et al., 2005) and increased vulnerability to infections (Aviles, Johnson, & Monroy, 2004; Takkouche, Regueira, & Gestal-Otero, 2001). Normal volunteers showed anxiety symptoms when injected with the immune activator lipopolysaccharide (Reichenberg et al., 2001). Several groups have reported a positive correlation between anxiety and inflammatory markers in humans (TNFα, IL-6, and CRP) (Arranz et al., 2007; Maes et al., 1998; Pitsavos et al., 2006). However, studies of Zorrilla, Redei, and DeRubeis (1994) have demonstrated a negative correlation. The inconsistency calls for a more extensive investigation including a larger sample size and a uniform sample selection excluding gender differences and other preexisting conditions.

Moving on the theme of involvement of unique neuroinflammatory cell-signaling cascades potentially critical to anxiety disorders, below we will discuss the role of oxidative stress within the CNS in regulation of anxiety phenotype.

4. INFLAMMATION IN ANXIETY DISORDERS: POTENTIAL ROLE OF OXIDATIVE STRESS

Oxidative stress is a state where the level of oxidants (hydrogen peroxide, superoxide, nitric oxide, etc.) produced by biological reactions exceeds the oxidants scavenging capacity of the cells. These oxidants modify cellular macromolecules (proteins, DNA, lipids) and alter cellular functions (Raha & Robinson, 2001). Increased oxidative damage most probably occurs in most if not all human diseases, although it perhaps plays a causal role only in a few. The role of oxidative stress in the development of neurodegenerative disorders is well reported (Greco & Fiskum, 2010; Lassmann, Brück, & Lucchinetti, 2001). Several theories have been proposed over the years to conceptualize the pathophysiology of anxiety disorders. Those theories include mechanisms such as impairment of neurotransmission,

genetic mutations, excitotoxicity, and stress. While most classical theories suggest involvement of traditional signal transduction mechanisms including abnormalities in the gamma amino butyric acid (GABA) and serotonin receptor systems in the etiology of anxiety, recent work from several labs (Bouayed, Rammal, & Soulimani, 2009; Bouayed, Rammal, Younos, & Soulimani, 2007; de Oliveira, Silvestrin, Mello, Souza, & Moreira, 2007; Hovatta et al., 2005; Masood, Nadeem, Mustafa, & O'Donnell, 2008; Souza et al., 2007) including our own published findings, has produced some provocative and interesting results, suggesting relevance of oxidative stress to anxiety disorders and implying that perhaps oxidative stress is the new stress as has been suggested previously (Gingrich, 2005).

Oxidative stress has been suggested to act as an initiator and/or a mediator of several human diseases. Increased oxidative and nitrosative stress triggered via generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), respectively, is reported to occur in several disorders of the CNS (Calabrese, Bates, & Stella, 2000; Halliwell, 2006; Sayre, Perry, & Smith, 2008). This association is largely due to the high vulnerability of brain to oxidative load (Ng, Berk, Dean, & Bush, 2008). Relevant to this, oxidative stress is reported to trigger chronic neuroinflammation, which is characterized by the generation of proinflammatory mediators locally produced by host cells, thus engaging the innate immune system. Both resident CNS cells and recruited leukocytes express various cytokines, major histocompatibility complex, and adhesion/costimulatory molecules, which collectively cause the generation of ROS (Floyd, 1999a, 1999b; Floyd et al., 1999; Hopkins & Rothwell, 1995; Martiney, Cuff, Litwak, Berman, & Brosnan, 1998; Merrill & Benveniste, 1996; Wakita, Shintani, Yagi, Asai, & Nozawa, 2001; Xiao & Link, 1998). ROS are highly toxic in the CNS when their production exceeds the neutralizing effects of endogenous antioxidants. Thus, the balance between pro- and anti-inflammatory factors determines the intensity and course of the inflammatory response including the levels of oxidative stress and consequent neurodegeneration (Bethea, 2000; Neumann, 2000; Sternberg, 1997; Stoll, Jander, & Schroeter, 2000; Streit, Walter, & Pennell, 1999). Neuroinflammation has been proposed to promote oxidative stress and contribute to irreversible neuronal dysfunction and cell death (Maccioni, Rojo, Fernandez, & Kuljis, 2009; Mhatre, Floyd, & Hensley, 2004), although neuroinflammation can be a cause as well as a consequence of chronic oxidative stress. Increased inflammation is reported to generate reactive oxygen and RNS in

ambient neurons (Apelt, Bigl, Wunderlich, & Schliebs, 2004; Mhatre et al., 2004). The proinflammatory cytokines IL-1β, IL-6, and TNF-α elicit immune responses in the CNS during inflammation (Hopkins & Rothwell, 1995; Martiney et al., 1998; Xiao & Link, 1998). They are potentially deleterious or beneficial, depending on their concentration, site, and duration of action (Bethea, 2000; Hermann, Rogers, Bresnahan, & Beattie, 2001; Longhi et al., 2001; Merrill & Benveniste, 1996; Sternberg, 1997; Stoll et al., 2000). Hence, excess or prolonged production of proinflammatory cytokines, such as in genetically manipulated mice, can lead to chronic inflammation and functional CNS-related disorders (Campbell, 1998a, 1998b; Campbell et al., 1993; Carrasco et al., 2000; Giralt et al., 2001; Probert, Akassoglou, Pasparakis, Kontogeorgos, & Kollias, 1995). New data show that direct induction of oxidative stress in male Sprague–Dawley rats via two separate oxidative stress inducers, X + XO (xanthine + xanthine oxidase) and BSO (buthionine sulfoximine), leads to increased CRP-1 and IL-6 in the serum and elevated TNF-α in the brain tissues of these rats (Salim et al., 2011). Interestingly, these rats have been reported to exhibit anxiety-like behavior in open-field and light–dark anxiety-like behavior tests (Salim et al., 2010a, 2010b). Anxiety-like behavior is linked to oxidative stress status not only in cerebral system but also in peripheral system in anxious mice. Rammal, Bouayed, Younos, and Soulimani (2008) report an imbalance in oxidative status in both neuronal and glial cells in the cerebellum and hippocampus, neurons of the cerebral cortex, and peripheral leucocytes in anxious mice and suggest a potential role of this redox system in the development of neuroinflammation and neurodegeneration. Relevant to this, activation of inflammatory pathways has been observed in patients with anxiety disorders (O'Donovan et al., 2010). Increased proinflammatory cytokines have also been detected in patients with major depression and anxiety disorders (Bob et al., 2010; O'Donovan et al., 2010). Particularly, increased IL-6 in depression (Bob et al., 2010) and anxiety disorder patients (O'Donovan et al., 2010) also has been reported. Multiple sclerosis is a disease of the CNS characterized by chronic inflammation and degenerative changes (Compston & Coles, 2008). Not surprisingly, the rate of affective disorders such as depression and anxiety is at least sixfold increased in this condition. In an animal model that mimics many aspects of multiple sclerosis (myelin oligodendrocyte glycoprotein experimental autoimmune encephalomyelitis), an increased anxiety-like behavior was displayed, which correlated with increase in hippocampal tissue TNF-α levels and neuronal loss (Peruga et al., 2011).