Published in final edited form as:
Exp Neurol. 2012 January ; 233(1): 40–48. doi:10.1016/j.expneurol.2010.11.014.

Dysregulated Neuronal-Microglial Cross-Talk during Aging, Stress and Inflammation

Heidi A. Jurgens[1,2] and **Rodney W. Johnson**[1,2,3,*]

[1]Neuroscience Program, University of Illinois, Urbana IL 61801

[2]Integrative Immunology and Behavior Program, University of Illinois, Urbana IL 61801

[3]Department of Animal Sciences, University of Illinois, Urbana IL 61801

Abstract

Communication between neurons and microglia is essential for maintaining homeostasis in the central nervous system (CNS) during both physiological and inflammatory conditions. While microglial activation is necessary and beneficial in response to injury or disease, excessive or prolonged activation can have deleterious effects on brain function and behavior. To prevent inflammation-associated damage, microglia reactivity is actively modulated by neurons in the healthy brain. Age or stress-induced disruption of normal neuronal-microglial communication could lead to an aberrant central immune response when additional stressors are applied. Recent work suggests that both aging and stress shift the CNS microenvironment to a pro-inflammatory state characterized by increased microglial reactivity and a reduction in anti-inflammatory and immunoregulatory factors. This review will discuss how heightened neuroinflammation associated with aging and stress may be compounded by the concomitant loss of neuronally derived factors that control microglial activation, leaving the brain vulnerable to excessive inflammation and neurobehavioral complications upon subsequent immune challenge.

INTRODUCTION

The job of the immune system is to detect and eliminate invading pathogens as well as repair damage and maintain tissue homeostasis. Essential to an organism's survival, the brain must be protected, but the typical inflammatory response used to eliminate pathogens or support healing in peripheral tissues can be destructive in the central nervous system (CNS). Inflammation in the brain must be tightly controlled to preserve the viability of neurons that are, for the most part, non-regenerative (Galea, et al., 2007). Although vulnerable, increasing evidence suggests that neurons are not the defenseless victims of excessive immune reaction, but rather are active players in CNS-immune interactions, carefully modulating mechanisms of microglial activation to maintain CNS integrity (Biber, et al., 2007). However, recent findings suggest that processes as ubiquitous as aging and stress can compromise normal neuronal control of microglial reactivity, decreasing the brain's resiliency to potential inflammatory insult.

*To whom correspondence should be addressed: 4 Animal Sciences Laboratory, 1207 W. Gregory Drive, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA. Tel: (217) 333-2118 Fax: (217) 244-2871, rwjohn@uiuc.edu .

The main focus of this review is to discuss the potential mechanisms underlying dysregulated neuronal-microglial cross-talk during aging and stress-induced neuroinflammation. Following a brief introduction to key concepts including immune-brain communication and the essential role of microglia in the CNS innate immune response, we will highlight recent findings suggesting that both aging and stress can induce microglial "priming", leading to an exaggerated and prolonged release of central cytokines upon additional immune stimulation. We then turn our focus on studies demonstrating that aging, stress and inflammation can impede neuronal regulatory mechanisms, including constitutively expressed immunomodulatory factors such as CD200 and CX3CL1 (fractalkine), which have been shown to play an important role in downregulating inflammatory processes. To conclude, we review evidence that aging and stress lead to deleterious alterations in the morphology and physiology of both neurons and microglia, and discuss how this concurrent decline in normal function can contribute to aberrant interactions under inflammatory conditions. Determining how neuroinflammatory processes can disrupt normal neuronal-microglia communication will contribute to a greater understanding of how microglial reactivity may be controlled or modulated following acute brain injury as well as during chronic neurological disease processes.

THE NEUROIMMUNE RESPONSE

Immune-Brain Communication

The bi-directional communication between the immune system and central nervous system (CNS) is critical for mounting an appropriate immunological, physiological and behavioral response to infection and injury. The host's first line of defense is the innate immune system. Innate immune cells, including macrophages in the periphery, and microglial cells in the CNS, detect potential insults via pattern-recognition receptors (PRRs) which recognize and respond to infectious elements (pathogen-associated molecular patterns, PAMPs), as well as endogenous danger signals induced by tissue damage (danger-associated molecular patterns, DAMPs) (Akira, et al., 2006, Matzinger, 2002). Upon activation, cells of the innate immune system synthesize and release cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) that serve as major mediators of the immune response.

Peripheral cytokines induced by the innate immune system act on the brain to induce nonspecific symptoms of infection including lethargy, listlessness, decreased activity and loss of interest in social interaction (Kelley, et al., 2003). This aspect of host defense has been termed the "sickness response" and includes changes in body temperature, increased sleep, reduction in food and water intake, and activation of the hypothalamic-pituitary-adrenal (HPA) axis (Dantzer and Kelley, 2007, Maier and Watkins, 1998). The physiological and behavioral aspects of the sickness response reflect the expression of an adaptive motivational state that resets the organism's priorities to promote resistance to pathogens and recovery from infection (Dantzer, 2001, Hart, 1988, Johnson, 2002). To induce a behavioral response, peripheral cytokines need to be able to exert their effects in the brain. Cytokines can access the brain via active transport mechanisms or diffusion at circumventricular organs (CVOs) where blood vessels lack a functional blood-brain barrier (Banks, et al., 2002, Konsman, et al., 1999). In addition, peripheral cytokines do not need to gain direct entry into the CNS because they can act at the blood-brain barrier to induce the synthesis and release of inflammatory mediators (cytokines and prostaglandins) from brain endothelial cells which then propagate the immune signal within the brain (Vitkovic, et al., 2000, Wong and Licinio, 1994). Finally, neural pathways (afferent vagus nerve) are directly responsive to peripheral cytokine stimulation, the signal then being transmitted to the CNS where it activates central effects including cytokine expression and sickness behavior (Goehler, et al., 1998, Luheshi GN, 2000). When cytokine signals from the peripheral

immune system reach the CNS, microglia become activated and propagate the inflammatory response throughout the brain.

Microglial Cells

Microglial cells comprise approximately 10-12% of the cells in the brain and predominate in the grey matter, with especially high concentrations in the hippocampus, hypothalamus, basal ganglia and substantia nigra (Block, et al., 2007, Lawson, et al., 1990, Mittelbronn, et al., 2001). Microglia normally exist in a quiescent or “resting” state in the healthy adult brain and are morphologically characterized by a small soma and long, thin (ramified) processes (Hanisch and Kettenmann, 2007). Although termed “resting”, microglia in the intact adult brain are not dormant. Highly motile microglial processes continuously scan the CNS microenvironment with estimates that the complete brain parenchyma is monitored every few hours (Davalos, et al., 2005, Nimmerjahn, et al., 2005). Even minor alterations in the CNS homeostasis alert microglia, allowing these cells to provide the first line of defense during infection, injury and disease.

In response to inflammatory stimuli, microglia are rapidly activated and undergo a morphological transformation with shorter, stouter processes (i.e.deramified) and larger soma size (Hanisch, 2002, Hanisch and Kettenmann, 2007, Long, et al., 1998). In addition, microglia upregulate cell surface molecules including major histocampatibility markers (MHC class I and II), receptors for cytokines and chemokines, and several other cellular markers indicative of increased reactivity (Lynch, 2009, Perry and Gordon, 1988). In response to a variety of stimuli, microglia can transform from a quiescent state to different activation states. The magnitude of microglial activation is influenced by the type and duration of the stimulus, the current CNS microenvironment and exposure to prior and existing stimuli (Perry, et al., 2007, Ransohoff and Perry, 2009, Schwartz, et al., 2006). Activated microglia release immune mediators that coordinate the response of both innate and adaptive immunity to control infection, remove cell debris and promote tissue repair (Kreutzberg, 1996, Neumann, et al., 2009, Streit, 2002).

Although microglial activation is necessary for host defense and neuroprotection, increased or prolonged activation can have detrimental and neurotoxic effects (Block, et al., 2007). One proposed mechanism for maintaining control of microglial activation is through interaction with neuronal signaling molecules. Healthy neurons maintain microglia in their resting state via secreted and membrane bound signals including CD200, CX3CL1 (fractalkine), neurotransmitters and neurotrophins (Biber, et al., 2007, Pocock and Kettenmann, 2007). A reduction in these regulatory factors can lead to a reactive microglia phenotype, suggesting an important role for communication between neurons and microglia in regulating neuroinflammation. During normal conditions, such signals efficiently regulate neuroimmune responses and help return the CNS microenvironment to a homeostatic state following insult. However, these neuromodulatory mechanisms may become deficient and/or dysregulated under excessive or prolonged inflammatory stimulation induced by disease and injury. While aging and stress are not considered “disease states”, both are associated with a heightened neuroinflammatory environment which can alter reciprocal interactions between microglia and neurons, resulting in a dysregulated response to immune stimuli.

AGING AND STRESS: A SHIFT TOWARDS NEUROINFLAMMATION

Aging

Recent experimental evidence suggests that the microenvironment of the normal aged brain is characterized by chronic low-level inflammation and increased microglia reactivity. Microglia with a phenotype of heightened reactivity are often referred to as “primed” or “sensitized,” due to a more rapid induction and greater cytokine release upon activation

when compared to normal microglia. Primed microglia appear to reside in a intermediate activation state, characterized by evidence of morphological activation (deramification) and upregulation of cell surface markers of activation (i.e. MHCII), but minimal basal production of pro-inflammatory cytokines (Perry, et al., 2007). Upon further stimulation induced by activation of the peripheral or central innate immune system, primed or sensitized microglia respond with pronounced and prolonged release of pro-inflammatory cytokines altering the course of action from physiological to pathological (Cunningham, et al., 2005, Dilger and Johnson, 2008). While microglia priming was first described in association with chronic neurodegenerative diseases including multiple sclerosis (MS), Alzheimer's disease (AD) and the murine ME7 model of prion disease (Perry, et al., 2003), increasing evidence suggests that primed or "sensitized" microglia may also reside in the normal aged brain (Bilbo, 2010, Frank, et al., 2006a, Godbout and Johnson, 2006, Sparkman and Johnson, 2008).

Several phenotypic and functional alterations indicative of increased microglial reactivity occur during the normal aging process. Microglial expression of MHCII, a marker of microglial activation, is increased in the aged but otherwise healthy brain of humans, non-human primates and rodents (Frank, et al., 2006a, Godbout, et al., 2005, Perry, et al., 1993, Sheffield and Berman, 1998, Streit and Sparks, 1997). Other cell surface markers including CD68, CD11b, the co-stimulatory molecules CD80 and CD86 and intercellular adhesion molecule-1 (ICAM-1) are also increased in the normal aged brain suggesting microglia cells acquire an activated immunophenotype (Downer, et al., 2010, Frank, et al., 2010a, Perry, et al., 1993). It is important to note that while these markers are used as indicators of microglia activation, they can also be expressed on other cells in the CNS, therefore up-regulation may not reflect changes in microglia alone (Lynch, 2009). However, new methods of rapid isolation of microglia from discrete brain regions allows for preservation of the *in vivo* phenotype of microglia allowing for functional characterization of microglia *ex vivo* in a controlled setting and devoid of other CNS cells (Frank, et al., 2006b). Recent studies using this method show that indeed microglia isolated from the aged rodent brain demonstrate basal upregulation of microglial markers of activation (MHCII, CD11b) (Frank, et al., 2010a, Henry, et al., 2009) and constitutively increased secretion of pro-inflammatory cytokines (Njie, et al., 2010). In addition to evidence of age-related activation, microglia from the aged brain also showed a significantly potentiated increase in pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) following *ex vivo* immune stimulation with the bacterial endotoxin lipopolysaccharide (LPS) (Frank, et al., 2010a, Henry, et al., 2009, Njie, et al., 2010). Overall, these studies allow for direct evidence of microglia-specific indices of altered reactivity and provide evidence that during normal aging a shift in the activation state of microglia sensitizes them to subsequent immune challenge.

Along with the age-associated increase in microglial reactivity, there is also an elevation in steady-state levels of pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α in the brain of normal aged rodents (Chen, et al., 2008, Godbout, et al., 2005, Maher, et al., 2005). Accompanying the age-related increase in pro-inflammatory cytokines, is a decrease in anti-inflammatory cytokines IL-10 and IL-4 (Frank, et al., 2006a, Maher, et al., 2005, Ye and Johnson, 2001). As both IL-10 and IL-4 can counteract the effects of inflammation by reducing the synthesis of pro-inflammatory cytokines and their receptors, a decline in these anti-inflammatory mediators may potentiate age-related neuroinflammation (Heyen, et al., 2000, Loane, et al., 2009, Sawada, et al., 1999, Strle, et al., 2001). These findings are consistent with data obtained from gene expression profiles of aged human and rodent brains showing that genes indicative of oxidative stress, inflammation and glial activation increase with age, while genes associated with synaptic function/transport, growth factors and trophic support decrease (Bishop, et al., 2010, Blalock, et al., 2003, Godbout, et al., 2005, Lee, et al., 2000).

A consequence of age-induced microglial priming is that an exaggerated inflammatory response occurs in the healthy aged brain following challenge with peripheral or central immune stimuli (Godbout, et al., 2005, Huang, et al., 2008). The prolonged increase in pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α in the aged brain is accompanied by an extended sickness response, impaired cognition and depressive behaviors (Abraham, et al., 2008, Chen, et al., 2008, Godbout, et al., 2008). Whereas sickness behavior is normally adaptive, the excessive production of cytokines in the aged brain can lead to pathological or maladaptive behavioral changes such as delayed recovery from sickness and cognitive impairment. The hippocampus has a high density of pro-inflammatory cytokine receptors, and appears to be particularly vulnerable to both aging- and inflammation-induced disruption in cognitive processing (Mattson and Magnus, 2006, Parnet, et al., 2002, Wilson, et al., 2002). Following activation of the peripheral innate immune system, aged rodents have significantly increased levels pro-inflammatory cytokines in the hippocampus and demonstrate deficits specific to hippocampal-associated learning and memory tasks when compared to adults (Abraham and Johnson, 2009, Barrientos, et al., 2006, Chen, et al., 2008, Rosczyk, et al., 2008). As pro-inflammatory cytokines can act directly on neurons in the hippocampus to impair synaptic plasticity, this may provide a possible mechanism underlying inflammation-induced cognitive impairment (Balschun, et al., 2004, Lynch, 2002, Pickering and O'Connor, 2007).

Stress

Systemic immune challenge and psychological stress provoke several common neurochemical changes including induction of pro-inflammatory cytokines in the brain, and activation of the hypothalamic-pituitary-adrenal (HPA) axis. While glucocorticoids, the major mammalian stress hormones (cortisol in humans and corticosterone in rodents), are generally considered anti-inflammatory, several studies have challenged this view. Glucocorticoids can either enhance or suppress immune function depending on several factors such as the concentration and duration (acute or chronic) of the stressor, as well as the timing of stress or stress hormone exposure relative to immune activation (Dhabhar, 2009, Sorrells, et al., 2009).

The effects of stress specific to neuroimmune function are complex, with evidence of both beneficial (neuroprotection and negative feedback on microglial activation) and detrimental (exacerbation of various aspects of neuroinflammation) actions (Glezer and Rivest, 2004, Sorrells and Sapolsky, 2007). In addition, recent studies have shown that cytokines and stressors can act synergistically, in which exposure to stress on a backdrop of immune activation, or conversely, immune challenge following a stressor, results in a potentiated cytokine response and alterations in sickness and cognitive behaviors (Anisman, 2009, Barrientos, et al., 2003, Frank, et al., 2010b, Gandhi, et al., 2007, Johnson, et al., 2004). For example, both acute and chronic stress administered prior to peripheral immune stimulus have been shown to potentiate the expression of pro-inflammatory cytokines in the hippocampus and frontal cortex of rodents (Johnson, et al., 2002, Munhoz, et al., 2006). In addition, both stress and administration of exogenous corticosterone have been shown to increase microglial reactivity, including up-regulation of microglial markers of activation (de Pablos, et al., 2006, Frank, et al., 2007, Frank, et al., 2010b) as well as proliferation (Nair and Bonneau, 2006), and morphological transformation of microglia from a resting to an activated state (Sugama, et al., 2007, Tynan, et al., 2010). Overall, the data suggest that similar to aging, certain types of stress can shift the neuroimmune microenvironment towards a pro-inflammatory state, resulting in an exaggerated response upon additional immune stimulation.

The response of the normal adult brain to stress-induced neuroinflammation greatly depends upon the type and duration of the stressor. Mild or naturalistic stressors such as forced swim

(Deak, et al., 2003), and predator odor (Plata-Salaman, et al., 2000), fail to induce brain cytokines, whereas more severe or chronic stress paradigms have been shown to activate microglia and induce central cytokine production (Deak, et al., 2005, Frank, et al., 2007, Nair and Bonneau, 2006, O'Connor, et al., 2003). While the neuroimmune response to stress is adaptive under normal conditions, preexisting inflammation can increase the vulnerability of the aged brain to the deleterious effects of even mild stressors. Recent data from our laboratory demonstrate that even in the absence of immune stimulation, mild psychological stress induces an amplified central cytokine response and prolonged cognitive impairment in aged animals (Buchanan, et al., 2008). Following short-term (30 min/day for 4 days) mild restraint stress, there was a significant increase in stress-induced microglial activation (upregulation of MHCII) and expression of IL-1β in the hippocampus of aged mice, but not adult mice (Figure 1). In addition, while working memory in the Morris water maze was disrupted for both adult and aged mice after the first day of stress, only aged mice continued to demonstrate stress-induced cognitive impairment on subsequent days of behavioral testing. It appears that aged mice are more sensitive to the neuroinflammatory and cognitive effects of stress and seem unable to adapt to the continued presence of a mild stressor (Buchanan, et al., 2008). Overall, these data as a whole suggest that both the aged and stressed brain may be primed to react to subsequent stimuli (both immunological and psychological) in a way that results in an exaggerated inflammatory response and excessive microglial activation.

MICROGLIA ESCAPE FROM NEURONAL CONTROL

While the exact mechanisms underlying microglia priming and activation during non-disease states remain unknown, increasing interest has turned to how universal conditions such as aging and stress can alter the brain microenvironment in a way that hinders the ability of neurons to control microglial activation. Microglia phenotype and function is highly influenced by the conditions of the CNS microenvironment and in particular, by specific interactions with surrounding neurons. While intense focus has been given to glial cell involvement in neuroinflammatory processes, the roles of neurons have been less examined, or even relegated to that of passive victims of overactive microglia. However, mechanisms of immune regulation in the CNS are largely dependent on neuronal viability and activity, providing compelling evidence that neurons themselves control microglial reactivity (Biber, et al., 2007, Tian, et al., 2009).

Fractalkine

Recent work has shown that the neuronally expressed chemokine, fractalkine, may be important in maintaining microglia in a resting state in the healthy brain as well as preventing excessive microglial activation during inflammatory conditions. Fractalkine (CX3CL1) is the sole member of the CXC subfamily of chemokines and exists as both a membrane-anchored ligand and a secreted glycoprotein suggesting that it can work locally, by direct contact, as well as through distant soluble effects (Bazan, et al., 1997). Fractalkine is one of a few chemokines that is constitutively expressed at high levels in the brain and is unique in that it binds only one receptor, CX3CR1 (Harrison, et al., 1998, Pan, et al., 1997). The widespread expression of fractalkine by neurons in the CNS along with complementary expression of its receptor on microglia, suggests that fractalkine plays an important physiological role in the communication between neurons and microglia (Cardona, et al., 2006, Harrison, et al., 1998).

Evidence from both *in vitro* and *in vivo* experiments demonstrates that interaction of fractalkine and its receptor contribute to attenuation of microglial activation and neurotoxicity under inflammatory conditions. *In vitro*, soluble fractalkine acts as an anti-inflammatory molecule via down-regulation of LPS-induced production of IL-1β, IL-6,

TNF-α, nitric oxide and iNOS in microglia and mixed glia cultures (Mizuno, et al., 2003, Zujovic, et al., 2000). Recent work has shown that both soluble and neuron-membrane bound fractalkine attenuate the LPS-induced increase in IL-1β and MHCII in primary microglial-neuronal cultures (Lyons, et al., 2009a). The addition of anti-fractalkine receptor antibody abrogates this effect indicating the CX3CL1-CX3CR1 interaction is necessary for modulation of microglial activation. *In vivo*, blocking endogenous fractalkine within the brain using an anti-fractalkine antibody potentiates the LPS-induced increase in hippocampal expression of TNF-α and 8-isoprostane (a marker of oxidative stress), suggesting that normal expression of fractalkine is necessary to control microglial activation (Zujovic, et al., 2001). Using mice lacking the microglial fractalkine receptor, it has been shown that the absence of CX3CL1-CX3CR1 signaling dysregulates microglial responses to both inflammatory and neurotoxic stimuli. CX3CR1-deficient mice show intense and widespread microglial activation as well as elevated production of IL-1β in the hippocampus in response to peripheral LPS injection (Cardona, et al., 2006)… In addition, in mouse models of Parkinson's disease and amyotrophic lateral sclerosis (ALS), CX3CR1-deficient mice had more pronounced microglial activation and extensive neuronal loss compared to wild-type controls (Cardona, et al., 2006). Overall these data suggest that during both acute inflammation and chronic neurodegeneration, CX3CL1-CX3CR1 interactions in the CNS function to attenuate excessive microglial activation.

Recently it has been shown that fractalkine is decreased in the hippocampus of aged rats (Bachstetter, et al., 2009, Lyons, et al., 2009a), as well in brain homogenates of aged mice (Wynne, et al., 2010). In these studies, decreased fractalkine corresponded with an age-related increase in markers of microglial activation including MHCII and CD40 as well as elevated microglial expression if IL-1β. Treatment of aged animals with central administration of fractalkine has been shown to attenuate both the age-related increase in microglial activation and deficit in LTP (Lyons, et al., 2009a), as well as reverse the decline in neurogenesis associated with aging (Bachstetter, et al., 2009). As administration of exogenous fractalkine can reduce age-associated neuroinflammation and restore neurogenesis, alteration in fractalkine signaling during normal aging appears to be due to reduced ligand levels. While it has been previously shown that LPS can reduce CX3CR1 *in vitro* (Boddeke, et al., 1999), a recent study was the first to show *in vivo* that peripheral LPS leads to a reduction CX3CR1 (both mRNA and surface expression) in microglia of both adult and aged mice (Wynne, et al., 2010). While CX3CR1 expression was depressed in both ages 4 hours after LPS injection, at 24 hours post-LPS, CX3CR1 expression was restored in adult mice while aged mice continued to show significant reduction. This protracted downregulation of CX3CR1 in aged mice corresponded with a prolonged induction of IL-1β and an extended sickness response. Together these data demonstrate that decreased fractalkine expression in the aged brain, along with failure to restore microglia CX3CR1 expression after it has been downregulated, contribute to impaired fractalkine-mediated regulation of microglia during normal aging (Wynne, et al., 2010).

CD200

Another factor known to play a role in modulating immune responses is the membrane glycoprotein CD200. CD200 is expressed on a wide variety of cell types including neurons and endothelial cells in the CNS whereas expression of its receptor, CD200R, is restricted predominantly to cells of myeloid origin including macrophages and microglia (Barclay, et al., 2002, Hoek, et al., 2000, Wright, et al., 2003). It has been suggested that interaction between neuronal CD200 and microglia-bound CD200R maintain microglia in a quiescent state (Hoek, et al., 2000, Neumann, 2001). Microglia of CD200-deficient mice spontaneously exhibit a more reactive phenotype, including less ramified and shorter processes, and increased expression of CD11b and CD45, suggesting that constitutive

interaction between CD200 and CD200R plays an important role in maintaining microglia in a resting state (Hoek, et al., 2000). Several studies have demonstrated that disruption of the CD200-CD200R interaction results in exaggerated and prolonged microglia activation and increased production of inflammatory mediators following immune challenge (Deckert, et al., 2006, Hoek, et al., 2000, Meuth, et al., 2008, Wright, et al., 2003)

In addition to its physiological role of maintaining microglia in a quiescent state in the intact CNS, CD200 may also play a neuroprotective role in chronic neurodegenerative diseases. While lack of CD200 signaling exacerbates neuroinflammation, enhanced CD200-CD200R signaling either via increased neuronal expression of CD200 or administration of the CD200R agonist CD200-Fc fusion protein, can down-regulate microglia activation, reduce pro-inflammatory cytokine expression and maintain neuronal integrity in the rodent experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS) (Chitnis, et al., 2007, Liu, et al., 2010). Recent findings in human patients also support the role of CD200 in regulating microglia activation in neuropathological conditions. Expression of CD200 has been found to be downregulated in lesions from the CNS of MS patients suggesting that the loss of CD200 permits enhanced inflammation, which may drive disease progression (Koning, et al., 2007, Koning, et al., 2009). Examination of postmortem brain tissue from Alzheimer's disease patients found that both CD200 and CD200R are significantly decreased in regions affected by AD pathology (hippocampus and inferior temporal gyrus) indicating an overall deficiency in the CD200-CD200R signaling system in regions where chronic inflammation is established (Walker, et al., 2009).

During normal brain aging, the age-related upregulation of microglial MHCII expression is accompanied by a significant decrease in the expression of CD200 in the hippocampus of healthy aged rodents suggesting that neuronal inhibition of microglial activation may become compromised with age (Frank, et al., 2006a, Lyons, et al., 2007). Recent evidence suggests that neuronal CD200 expression may be modulated by IL-4, an anti-inflammatory cytokine shown to modulate microglial activation (Downer, et al., 2010, Lyons, et al., 2009b). As both IL-4 and CD200 expression is decreased in the hippocampus of aged it is likely that the concomitant reduction in these factors contributes to increased microglial reactivity (Lynch, 2009, Nolan, et al., 2005). In addition, treatment of aged rats with the NCAM mimetic FG loop (FGL) peptide reverses the age-related decline in hippocampal CD200 expression and subsequently attenuates the age-related increase in markers of microglial activation (CD86, ICAM, CD40 and MHCII) and inflammation (IL-1β and IFN-γ) (Downer, et al., 2009, Downer, et al., 2010). In a model of postoperative cognitive decline, aged, but not adult, rodents have increased expression of pro-inflammatory cytokines in the hippocampus and deficits in hippocampal-dependent cognition following abdominal surgery (Cao, et al., 2010, Rosczyk, et al., 2008). In addition, hippocampal CD200 is downregulated postoperatively, suggesting that age-related neuroinflammation following surgical trauma may be mediated in part by decreased immunoregulatory control of microglia (Cao, et al., 2010).

In experiments designed to elucidate the potential mechanisms underlying stress-induced sensitization of microglia it was found that 24 hours following inescapable stress, rats had significantly decreased hippocampal expression of CD200, while MHCII expression and LPS-induced cytokine production was significantly increased in hippocampal microglia (Frank, et al., 2007). As both aging and stress reduce CD200 expression in the hippocampus this could contribute to attenuated neuronal control of microglia resulting in a permissive pro-inflammatory CNS microenvironment and aberrant neuroimmune response upon additional immune stimulation.

Similar to the CD200-CD200R interaction, the constitutive expression of CD47 and CD22 on neurons is also thought to play a role in keeping microglia quiescent via interaction with microglial receptors SIRP-α and CD45. (Barclay, et al., 2002, Biber, et al., 2007, Mott, et al., 2004, Tian, et al., 2009). Neurons can also secrete CD22 which acts as an anti-inflammatory neuropeptide, reducing LPS-induced microglial activation and pro-inflammatory cytokine production (Mott, et al., 2004). In this study it was demonstrated that neurons must have functional axon terminals for this inhibition to occur, suggesting that physiologically intact neurons are necessary for the regulation of microglial activation.

INFLAMMATORY DISRUPTION OF NEURONAL-MICROGLIAL INTERACTION

Neuronal Integrity

In addition to controlling microglial activity via immunomodulatory factors, the normal physiological activity of neurons is a key negative regulator of the CNS immune response. Functionally active neurons release a number of soluble mediators including neurotransmitters and neurotrophic factors that keep microglia in a resting state (Neumann, 2001, Pocock and Kettenmann, 2007). Even relatively minor deviations from normal neuronal activity seem to be sufficient to alert microglia, which express several neurotransmitter and neurotrophic factors allowing for response to alterations in the neuronal network integrity (Hanisch and Kettenmann, 2007, Pocock and Kettenmann, 2007, Schwartz, et al., 2006). Control of microglial reactivity by healthy functional neurons was demonstrated in hippocampal slice culture in which blockade of spontaneous neuronal activity resulted in increased microglial expression of MHCII (Neumann, et al., 1996). It was further demonstrated that brain-derived neurotrophic factor (BDNF), nerve-growth factor (NGF) and neurotrophin-3 (NT-3) secreted by electrically active neurons can inhibit the induction of MCHII expression in microglia (Neumann, et al., 1998).

If healthy functional neurons have a generally suppressive potential that helps to maintain microglia in a resting state, then it follows that the loss of physiological activity due to impaired function or atrophy of neurons could contribute to increased microglial activation and inflammation. In several states including exposure to chronic stress, normal aging, and in neuropathologies including Alzheimer's disease, schizophrenia and depression, there is a demonstrated neuroinflammatory component along with reduced neurotrophic support and evidence of neuronal atrophy (Angelucci, et al., 2005, Dantzer, et al., 2008, Godbout and Johnson, 2006, Lupien, et al., 2009, Smith, et al., 1995, Tapia-Arancibia, et al., 2008). A reduction in normal neuronal function could allow microglia to escape regulatory control leading to excessive microglial activation and increased inflammation-induced neuronal damage (Figure 2).

Evidence for cytokine-induced dendritic atrophy comes from both *in vitro* and *in vivo* studies. In neuron culture, supernatant from LPS-activated microglia prevented neurite outgrowth and TNF-α was shown to induce the retraction of already extended dendrites (Munch, et al., 2003, Neumann, et al., 2002). In mice injected centrally with LPS, there was significant degeneration of spines and reduced dendritic branching in hippocampal pyramidal neurons without a corresponding loss of neuron number (Milatovic, et al., 2003). A mechanism by which inflammatory stimuli may alter hippocampal structure and function is via inhibition of neurotrophins which are known to modulate axon and dendrite morphology, synaptic plasticity and memory formation (Chao, 2003, Poo, 2001, Tyler, et al., 2002). Recent data from our lab have shown that aged mice injected peripherally with LPS have an exaggerated neuroinflammatory response that is accompanied by decreased BDNF and NGF and dendritic atrophy of hippocampal neurons (Richwine, et al., 2008). The association amongst increased inflammatory factors and reduced neurotrophins is not just correlational, as it has been shown in neuron culture that IL-1β directly interferes with both

BDNF and NT-3 signaling pathways (Soiampornkul, et al., 2008, Tong, et al., 2008). Furthermore, *in vivo*, BDNF, NGF and NT-3 protein levels were significantly reduced (20-40%) in the hippocampus and cortex for 7 days following peripheral LPS injection in rats (Guan and Fang, 2006). As such, pro-inflammatory cytokines induced by aging, stress or inflammation could disrupt neuronal functions that are normally maintained by neurotrophins, thus leaving the brain vulnerable to the detrimental effects of subsequent inflammation.

Microglial Dysfunction

The bi-directional communication between neurons and microglia plays an important role in regulating the neuroimmune response. Therefore, any alteration in the normal function of either of these populations could have detrimental consequences. While it is well accepted that neuronal function can decline with age, it has been suggested that microglia "age" as well, with concomitant degeneration of normal structure and function (Conde and Streit, 2006). As such, the role of microglia in aging and neurodegeneration may not be restricted to a gain of inflammatory function, but may also include the loss of protective and neurotrophic functions due to microglia senescence and dysfunction.

Microglia in both the resting and activated state serve beneficial roles including monitoring the functional state of neuronal synapses, supporting neurogenesis and clearing tissue debris to facilitate regeneration (Neumann, et al., 2009, Wake, et al., 2009, Ziv and Schwartz, 2008). Dysfunctional or senescent microglia are less able to carry out their neuroprotective functions and may fail to respond appropriately or efficiently to immune stimuli, leading to an overall less protective CNS microenvironment and increased neuronal vulnerability to age-related neurodegeneration (Streit, et al., 2008). Whether heightened neuroinflammation associated with aging promotes neurodegeneration or, whether insufficient immune responses during normal aging contribute to disease progression, remains an unresolved and fundamental issue (Lucin and Wyss-Coray, 2009). The concept of microglial dystrophy widens the perspective on the role of microglia during aging and age-related neurodegenerative disease in that both microglial activation, as well as microglial dysfunction, can contribute to the dysregulated relationship between neurons and microglia (Graeber and Streit, 2010).

CONCLUSION

Overall, it is clear that bi-directional communication between neurons and microglia is essential in maintaining homeostasis in the CNS as well as responding appropriately to a variety of neuroimmune challenges. However, neurons are not simply bystanders to the effects of microglial activation but instead play an active role in modulating microglia phenotype and function. Changes in the physiology, morphology and function of neurons and microglia under conditions of aging, stress and inflammation disrupt the normal cross-talk between these cells in resulting in a dysregulated neuroimmune environment with potential deleterious consequences on brain function and behavior. While both increased microglia activation and neuronal injury can be the result of an exaggerated neuroimmune response, it is unknown if microglial overactivation precedes and causes neuronal damage, or if activation occurs in response to loss of normal neuronal integrity. As opposed to simple cause and effect, complex interactions between neurons and microglia may predominate. While the focus of this review is on neuronal-microglial interactions, there is much evidence that other cells of the CNS and immune system, including astrocytes and T cells, interact with microglia and neurons in both normal and pathological states (Barres, 2008, Schwartz and Ziv, 2008, Tian, et al., 2009). Neuroimmune function during health, aging and disease is determined by the maintenance (or disruption) of the intricate balance of pro-inflammatory and anti-inflammatory mediators produced by a variety of cell types. A greater

understanding of the neuroregulatory systems governing complex cell-cell communication in the CNS, such as the cross-talk between neurons and microglia, is of crucial interest as clarification of the mechanisms underlying these interactions can lead to therapeutic interventions for a number of neurological diseases.

Acknowledgments

This work was supported by NIH grant AG016710.

REFERENCES

1. Abraham J, Jang S, Godbout JP, Chen J, Kelley KW, Dantzer R, Johnson RW. Aging sensitizes mice to behavioral deficits induced by central HIV-1 gp120. Neurobiol Aging. 2008; 29:614–621. [PubMed: 17174449]
2. Abraham J, Johnson RW. Consuming a diet supplemented with resveratrol reduced infection-related neuroinflammation and deficits in working memory in aged mice. Rejuvenation Res. 2009; 12:445–453. [PubMed: 20041738]
3. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006; 124:783–801. [PubMed: 16497588]
4. Angelucci F, Brene S, Mathe AA. BDNF in schizophrenia, depression and corresponding animal models. Mol Psychiatry. 2005; 10:345–352. [PubMed: 15655562]
5. Anisman H. Cascading effects of stressors and inflammatory immune system activation: implications for major depressive disorder. J Psychiatry Neurosci. 2009; 34:4–20. [PubMed: 19125209]
6. Bachstetter AD, Morganti JM, Jernberg J, Schlunk A, Mitchell SH, Brewster KW, Hudson CE, Cole MJ, Harrison JK, Bickford PC, Gemma C. Fractalkine and CX(3)CR1 regulate hippocampal neurogenesis in adult and aged rats. Neurobiol Aging. 2009
7. Balschun D, Wetzel W, Del Rey A, Pitossi F, Schneider H, Zuschratter W, Besedovsky HO. Interleukin-6: a cytokine to forget. FASEB J. 2004; 18:1788–1790. [PubMed: 15345694]
8. Banks WA, Farr SA, Morley JE. Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes. Neuroimmunomodulation. 2002; 10:319–327. [PubMed: 12907838]
9. Barclay AN, Wright GJ, Brooke G, Brown MH. CD200 and membrane protein interactions in the control of myeloid cells. Trends Immunol. 2002; 23:285–290. [PubMed: 12072366]
10. Barres BA. The mystery and magic of glia: a perspective on their roles in health and disease. Neuron. 2008; 60:430–440. [PubMed: 18995817]
11. Barrientos RM, Higgins EA, Biedenkapp JC, Sprunger DB, Wright-Hardesty KJ, Watkins LR, Rudy JW, Maier SF. Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol Aging. 2006; 27:723–732. [PubMed: 15893410]
12. Barrientos RM, Sprunger DB, Campeau S, Higgins EA, Watkins LR, Rudy JW, Maier SF. Brain-derived neurotrophic factor mRNA downregulation produced by social isolation is blocked by intrahippocampal interleukin-1 receptor antagonist. Neuroscience. 2003; 121:847–853. [PubMed: 14580934]
13. Bazan JF, Bacon KB, Hardiman G, Wang W, Soo K, Rossi D, Greaves DR, Zlotnik A, Schall TJ. A new class of membrane-bound chemokine with a CX3C motif. Nature. 1997; 385:640–644. [PubMed: 9024663]
14. Biber K, Neumann H, Inoue K, Boddeke HW. Neuronal ‘On’ and ‘Off’ signals control microglia. Trends Neurosci. 2007; 30:596–602. [PubMed: 17950926]
15. Bilbo SD. Early-life infection is a vulnerability factor for aging-related glial alterations and cognitive decline. Neurobiol Learn Mem. 2010; 94:57–64. [PubMed: 20388544]
16. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature. 2010; 464:529–535. [PubMed: 20336135]
17. Blalock EM, Chen KC, Sharrow K, Herman JP, Porter NM, Foster TC, Landfield PW. Gene microarrays in hippocampal aging: statistical profiling identifies novel processes correlated with cognitive impairment. J Neurosci. 2003; 23:3807–3819. [PubMed: 12736351]

18. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007; 8:57–69. [PubMed: 17180163]
19. Boddeke EW, Meigel I, Frentzel S, Biber K, Renn LQ, Gebicke-Harter P. Functional expression of the fractalkine (CX3C) receptor and its regulation by lipopolysaccharide in rat microglia. Eur J Pharmacol. 1999; 374:309–313. [PubMed: 10422773]
20. Buchanan JB, Sparkman NL, Chen J, Johnson RW. Cognitive and neuroinflammatory consequences of mild repeated stress are exacerbated in aged mice. Psychoneuroendocrinology. 2008; 33:755–765. [PubMed: 18407425]
21. Cao XZ, Ma H, Wang JK, Liu F, Wu BY, Tian AY, Wang LL, Tan WF. Postoperative cognitive deficits and neuroinflammation in the hippocampus triggered by surgical trauma are exacerbated in aged rats. Prog Neuropsychopharmacol Biol Psychiatry. 2010 Epub Aug 4.
22. Cardona AE, Pioro EP, Sasse ME, Kostenko V, Cardona SM, Dijkstra IM, Huang D, Kidd G, Dombrowski S, Dutta R, Lee JC, Cook DN, Jung S, Lira SA, Littman DR, Ransohoff RM. Control of microglial neurotoxicity by the fractalkine receptor. Nat Neurosci. 2006; 9:917–924. [PubMed: 16732273]
23. Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci. 2003; 4:299–309. [PubMed: 12671646]
24. Chen J, Buchanan JB, Sparkman NL, Godbout JP, Freund GG, Johnson RW. Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral innate immune system. Brain Behav Immun. 2008; 22:301–311. [PubMed: 17951027]
25. Chitnis T, Imitola J, Wang Y, Elyaman W, Chawla P, Sharuk M, Raddassi K, Bronson RT, Khoury SJ. Elevated neuronal expression of CD200 protects Wlds mice from inflammation-mediated neurodegeneration. Am J Pathol. 2007; 170:1695–1712. [PubMed: 17456775]
26. Conde JR, Streit WJ. Microglia in the aging brain. J Neuropathol Exp Neurol. 2006; 65:199–203. [PubMed: 16651881]
27. Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. J Neurosci. 2005; 25:9275–9284. [PubMed: 16207887]
28. Dantzer R. Cytokine-induced sickness behavior: where do we stand? Brain Behav Immun. 2001; 15:7–24. [PubMed: 11259077]
29. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007; 21:153–160. [PubMed: 17088043]
30. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008; 9:46–56. [PubMed: 18073775]
31. Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB. ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci. 2005; 8:752–758. [PubMed: 15895084]
32. de Pablos RM, Villaran RF, Arguelles S, Herrera AJ, Venero JL, Ayala A, Cano J, Machado A. Stress increases vulnerability to inflammation in the rat prefrontal cortex. J Neurosci. 2006; 26:5709–5719. [PubMed: 16723527]
33. Deak T, Bellamy C, D'Agostino LG. Exposure to forced swim stress does not alter central production of IL-1. Brain Res. 2003; 972:53–63. [PubMed: 12711078]
34. Deak T, Bordner KA, McElderry NK, Barnum CJ, Blandino P Jr. Deak MM, Tammariello SP. Stress-induced increases in hypothalamic IL-1: a systematic analysis of multiple stressor paradigms. Brain Res Bull. 2005; 64:541–556. [PubMed: 15639551]
35. Deckert M, Sedgwick JD, Fischer E, Schluter D. Regulation of microglial cell responses in murine Toxoplasma encephalitis by CD200/CD200 receptor interaction. Acta Neuropathol. 2006; 111:548–558. [PubMed: 16718351]
36. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation. 2009; 16:300–317. [PubMed: 19571591]

37. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol. 2008; 84:932–939. [PubMed: 18495785]
38. Downer EJ, Cowley TR, Cox F, Maher FO, Berezin V, Bock E, Lynch MA. A synthetic NCAM-derived mimetic peptide, FGL, exerts anti-inflammatory properties via IGF-1 and interferon-gamma modulation. J Neurochem. 2009; 109:1516–1525. [PubMed: 19457161]
39. Downer EJ, Cowley TR, Lyons A, Mills KH, Berezin V, Bock E, Lynch MA. A novel anti-inflammatory role of NCAM-derived mimetic peptide, FGL. Neurobiol Aging. 2010; 31:118–128. [PubMed: 18468731]
40. Frank MG, Baratta MV, Sprunger DB, Watkins LR, Maier SF. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. Brain Behav Immun. 2007; 21:47–59. [PubMed: 16647243]
41. Frank MG, Barrientos RM, Biedenkapp JC, Rudy JW, Watkins LR, Maier SF. mRNA up-regulation of MHC II and pivotal pro-inflammatory genes in normal brain aging. Neurobiol Aging. 2006a; 27:717–722. [PubMed: 15890435]
42. Frank MG, Barrientos RM, Watkins LR, Maier SF. Aging sensitizes rapidly isolated hippocampal microglia to LPS ex vivo. J Neuroimmunol. 2010a; 226:181–184. [PubMed: 20537730]
43. Frank MG, Miguel ZD, Watkins LR, Maier SF. Prior exposure to glucocorticoids sensitizes the neuroinflammatory and peripheral inflammatory responses to E. coli lipopolysaccharide. Brain Behav Immun. 2010b; 24:19–30. [PubMed: 19647070]
44. Frank MG, Wieseler-Frank JL, Watkins LR, Maier SF. Rapid isolation of highly enriched and quiescent microglia from adult rat hippocampus: immunophenotypic and functional characteristics. J Neurosci Methods. 2006b; 151:121–130. [PubMed: 16125247]
45. Galea I, Bechmann I, Perry VH. What is immune privilege (not)? Trends Immunol. 2007; 28:12–18. [PubMed: 17129764]
46. Gandhi R, Hayley S, Gibb J, Merali Z, Anisman H. Influence of poly I:C on sickness behaviors, plasma cytokines, corticosterone and central monoamine activity: moderation by social stressors. Brain Behav Immun. 2007; 21:477–489. [PubMed: 17267173]
47. Glezer I, Rivest S. Glucocorticoids: protectors of the brain during innate immune responses. Neuroscientist. 2004; 10:538–552. [PubMed: 15534039]
48. Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, Johnson RW. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. Faseb J. 2005; 19:1329–1331. [PubMed: 15919760]
49. Godbout JP, Johnson RW. Age and neuroinflammation: a lifetime of psychoneuroimmune consequences. Neurol Clin. 2006; 24:521–538. [PubMed: 16877122]
50. Godbout JP, Moreau M, Lestage J, Chen J, Sparkman NL, J OC, Castanon N, Kelley KW, Dantzer R, Johnson RW. Aging exacerbates depressive-like behavior in mice in response to activation of the peripheral innate immune system. Neuropsychopharmacology. 2008; 33:2341–2351. [PubMed: 18075491]
51. Goehler LE, Gaykema RP, Hammack SE, Maier SF, Watkins LR. Interleukin-1 induces c-Fos immunoreactivity in primary afferent neurons of the vagus nerve. Brain Res. 1998; 804:306–310. [PubMed: 9757071]
52. Graeber MB, Streit WJ. Microglia: biology and pathology. Acta Neuropathol. 2010; 119:89–105. [PubMed: 20012873]
53. Guan Z, Fang J. Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. Brain Behav Immun. 2006; 20:64–71. [PubMed: 15922558]
54. Hanisch UK. Microglia as a source and target of cytokines. Glia. 2002; 40:140–155. [PubMed: 12379902]
55. Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci. 2007; 10:1387–1394. [PubMed: 17965659]
56. Harrison JK, Jiang Y, Chen S, Xia Y, Maciejewski D, McNamara RK, Streit WJ, Salafranca MN, Adhikari S, Thompson DA, Botti P, Bacon KB, Feng L. Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1- expressing microglia. Proc Natl Acad Sci U S A. 1998; 95:10896–10901. [PubMed: 9724801]

57. Hart BL. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev. 1988; 12:123–137. [PubMed: 3050629]
58. Henry CJ, Huang Y, Wynne AM, Godbout JP. Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1beta and anti-inflammatory IL-10 cytokines. Brain Behav Immun. 2009; 23:309–317. [PubMed: 18814846]
59. Heyen JR, Ye S, Finck BN, Johnson RW. Interleukin (IL)-10 inhibits IL-6 production in microglia by preventing activation of NF-kappaB. Brain Res Mol Brain Res. 2000; 77:138–147. [PubMed: 10814840]
60. Hoek RM, Ruuls SR, Murphy CA, Wright GJ, Goddard R, Zurawski SM, Blom B, Homola ME, Streit WJ, Brown MH, Barclay AN, Sedgwick JD. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). Science. 2000; 290:1768–1771. [PubMed: 11099416]
61. Huang Y, Henry CJ, Dantzer R, Johnson RW, Godbout JP. Exaggerated sickness behavior and brain proinflammatory cytokine expression in aged mice in response to intracerebroventricular lipopolysaccharide. Neurobiol Aging. 2008; 29:1744–1753. [PubMed: 17543422]
62. Johnson JD, O'Connor KA, Deak T, Stark M, Watkins LR, Maier SF. Prior stressor exposure sensitizes LPS-induced cytokine production. Brain Behav Immun. 2002; 16:461–476. [PubMed: 12096891]
63. Johnson JD, O'Connor KA, Watkins LR, Maier SF. The role of IL-1beta in stress-induced sensitization of proinflammatory cytokine and corticosterone responses. Neuroscience. 2004; 127:569–577. [PubMed: 15283957]
64. Johnson RW. The concept of sickness behavior: a brief chronological account of four key discoveries. Vet Immunol Immunopathol. 2002; 87:443–450. [PubMed: 12072271]
65. Kelley KW, Bluthe RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, Broussard SR. Cytokine-induced sickness behavior. Brain Behav Immun. 2003; 17(Suppl 1):S112–118. [PubMed: 12615196]
66. Koning N, Bo L, Hoek RM, Huitinga I. Downregulation of macrophage inhibitory molecules in multiple sclerosis lesions. Ann Neurol. 2007; 62:504–514. [PubMed: 17879969]
67. Koning N, Swaab DF, Hoek RM, Huitinga I. Distribution of the immune inhibitory molecules CD200 and CD200R in the normal central nervous system and multiple sclerosis lesions suggests neuron-glia and glia-glia interactions. J Neuropathol Exp Neurol. 2009; 68:159–167. [PubMed: 19151626]
68. Konsman JP, Kelley K, Dantzer R. Temporal and spatial relationships between lipopolysaccharide-induced expression of Fos, interleukin-1beta and inducible nitric oxide synthase in rat brain. Neuroscience. 1999; 89:535–548. [PubMed: 10077334]
69. Kreutzberg GW. Microglia: a sensor for pathological events in the CNS. Trends Neurosci. 1996; 19:312–318. [PubMed: 8843599]
70. Lawson LJ, Perry VH, Dri P, Gordon S. Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. Neuroscience. 1990; 39:151–170. [PubMed: 2089275]
71. Lee CK, Weindruch R, Prolla TA. Gene-expression profile of the ageing brain in mice. Nat Genet. 2000; 25:294–297. [PubMed: 10888876]
72. Liu Y, Bando Y, Vargas-Lowy D, Elyaman W, Khoury SJ, Huang T, Reif K, Chitnis T. CD200R1 agonist attenuates mechanisms of chronic disease in a murine model of multiple sclerosis. J Neurosci. 2010; 30:2025–2038. [PubMed: 20147531]
73. Loane DJ, Deighan BF, Clarke RM, Griffin RJ, Lynch AM, Lynch MA. Interleukin-4 mediates the neuroprotective effects of rosiglitazone in the aged brain. Neurobiol Aging. 2009; 30:920–931. [PubMed: 17950491]
74. Long JM, Kalehua AN, Muth NJ, Hengemihle JM, Jucker M, Calhoun ME, Ingram DK, Mouton PR. Stereological estimation of total microglia number in mouse hippocampus. J Neurosci Methods. 1998; 84:101–108. [PubMed: 9821640]
75. Lucin KM, Wyss-Coray T. Immune activation in brain aging and neurodegeneration: too much or too little? Neuron. 2009; 64:110–122. [PubMed: 19840553]

76. Luheshi GN, B. R, Rushforth D, Mulcahy N, Konsman JP, Goldbach M, Dantzer R. Vagotomy attenuates the behavioural but not the pyrogenic effects of interleukin-1 in rats. Auton Neurosci. 2000; 85:127–132. [PubMed: 11189019]
77. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009; 10:434–445. [PubMed: 19401723]
78. Lynch MA. Interleukin-1 beta exerts a myriad of effects in the brain and in particular in the hippocampus: analysis of some of these actions. Vitam Horm. 2002; 64:185–219. [PubMed: 11898392]
79. Lynch MA. The multifaceted profile of activated microglia. Mol Neurobiol. 2009; 40:139–156. [PubMed: 19629762]
80. Lyons A, Downer EJ, Crotty S, Nolan YM, Mills KH, Lynch MA. CD200 ligand receptor interaction modulates microglial activation in vivo and in vitro: a role for IL-4. J Neurosci. 2007; 27:8309–8313. [PubMed: 17670977]
81. Lyons A, Lynch AM, Downer EJ, Hanley R, O'Sullivan JB, Smith A, Lynch MA. Fractalkine-induced activation of the phosphatidylinositol-3 kinase pathway attentuates microglial activation in vivo and in vitro. J Neurochem. 2009a; 110:1547–1556. [PubMed: 19627440]
82. Lyons A, McQuillan K, Deighan BF, O'Reilly JA, Downer EJ, Murphy AC, Watson M, Piazza A, O'Connell F, Griffin R, Mills KH, Lynch MA. Decreased neuronal CD200 expression in IL-4-deficient mice results in increased neuroinflammation in response to lipopolysaccharide. Brain Behav Immun. 2009b; 23:1020–1027. [PubMed: 19501645]
83. Maher FO, Nolan Y, Lynch MA. Downregulation of IL-4-induced signalling in hippocampus contributes to deficits in LTP in the aged rat. Neurobiol Aging. 2005; 26:717–728. [PubMed: 15708447]
84. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev. 1998; 105:83–107. [PubMed: 9450372]
85. Mattson MP, Magnus T. Ageing and neuronal vulnerability. Nat Rev Neurosci. 2006; 7:278–294. [PubMed: 16552414]
86. Matzinger P. An innate sense of danger. Ann N Y Acad Sci. 2002; 961:341–342. [PubMed: 12081934]
87. Meuth SG, Simon OJ, Grimm A, Melzer N, Herrmann AM, Spitzer P, Landgraf P, Wiendl H. CNS inflammation and neuronal degeneration is aggravated by impaired CD200-CD200R-mediated macrophage silencing. J Neuroimmunol. 2008; 194:62–69. [PubMed: 18164423]
88. Milatovic D, Zaja-Milatovic S, Montine KS, Horner PJ, Montine TJ. Pharmacologic suppression of neuronal oxidative damage and dendritic degeneration following direct activation of glial innate immunity in mouse cerebrum. J Neurochem. 2003; 87:1518–1526. [PubMed: 14713307]
89. Mittelbronn M, Dietz K, Schluesener HJ, Meyermann R. Local distribution of microglia in the normal adult human central nervous system differs by up to one order of magnitude. Acta Neuropathol. 2001; 101:249–255. [PubMed: 11307625]
90. Mizuno T, Kawanokuchi J, Numata K, Suzumura A. Production and neuroprotective functions of fractalkine in the central nervous system. Brain Res. 2003; 979:65–70. [PubMed: 12850572]
91. Mott RT, Ait-Ghezala G, Town T, Mori T, Vendrame M, Zeng J, Ehrhart J, Mullan M, Tan J. Neuronal expression of CD22: novel mechanism for inhibiting microglial proinflammatory cytokine production. Glia. 2004; 46:369–379. [PubMed: 15095367]
92. Munch G, Gasic-Milenkovic J, Dukic-Stefanovic S, Kuhla B, Heinrich K, Riederer P, Huttunen HJ, Founds H, Sajithlal G. Microglial activation induces cell death, inhibits neurite outgrowth and causes neurite retraction of differentiated neuroblastoma cells. Exp Brain Res. 2003; 150:1–8. [PubMed: 12698210]
93. Munhoz CD, Lepsch LB, Kawamoto EM, Malta MB, Lde S. Lima, Avellar MC, Sapolsky RM, Scavone C. Chronic unpredictable stress exacerbates lipopolysaccharide-induced activation of nuclear factor-kappaB in the frontal cortex and hippocampus via glucocorticoid secretion. J Neurosci. 2006; 26:3813–3820. [PubMed: 16597735]
94. Nair A, Bonneau RH. Stress-induced elevation of glucocorticoids increases microglia proliferation through NMDA receptor activation. J Neuroimmunol. 2006; 171:72–85. [PubMed: 16278020]

95. Neumann H. Control of glial immune function by neurons. Glia. 2001; 36:191–199. [PubMed: 11596127]
96. Neumann H, Boucraut J, Hahnel C, Misgeld T, Wekerle H. Neuronal control of MHC class II inducibility in rat astrocytes and microglia. Eur J Neurosci. 1996; 8:2582–2590. [PubMed: 8996807]
97. Neumann H, Kotter MR, Franklin RJ. Debris clearance by microglia: an essential link between degeneration and regeneration. Brain. 2009; 132:288–295. [PubMed: 18567623]
98. Neumann H, Misgeld T, Matsumuro K, Wekerle H. Neurotrophins inhibit major histocompatibility class II inducibility of microglia: involvement of the p75 neurotrophin receptor. Proc Natl Acad Sci U S A. 1998; 95:5779–5784. [PubMed: 9576961]
99. Neumann H, Schweigreiter R, Yamashita T, Rosenkranz K, Wekerle H, Barde YA. Tumor necrosis factor inhibits neurite outgrowth and branching of hippocampal neurons by a rho-dependent mechanism. J Neurosci. 2002; 22:854–862. [PubMed: 11826115]
100. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005; 308:1314–1318. [PubMed: 15831717]
101. Njie EG, Boelen E, Stassen FR, Steinbusch HW, Borchelt DR, Streit WJ. Ex vivo cultures of microglia from young and aged rodent brain reveal age-related changes in microglial function. Neurobiol Aging. 2010 Epub Jun 25.
102. Nolan Y, Maher FO, Martin DS, Clarke RM, Brady MT, Bolton AE, Mills KH, Lynch MA. Role of interleukin-4 in regulation of age-related inflammatory changes in the hippocampus. J Biol Chem. 2005; 280:9354–9362. [PubMed: 15615726]
103. O'Connor KA, Johnson JD, Hansen MK, Frank J. L. Wieseler, Maksimova E, Watkins LR, Maier SF. Peripheral and central proinflammatory cytokine response to a severe acute stressor. Brain Res. 2003; 991:123–132. [PubMed: 14575884]
104. Pan Y, Lloyd C, Zhou H, Dolich S, Deeds J, Gonzalo JA, Vath J, Gosselin M, Ma J, Dussault B, Woolf E, Alperin G, Culpepper J, Gutierrez-Ramos JC, Gearing D. Neurotactin, a membrane-anchored chemokine upregulated in brain inflammation. Nature. 1997; 387:611–617. [PubMed: 9177350]
105. Parnet P, Kelley KW, Bluthe RM, Dantzer R. Expression and regulation of interleukin-1 receptors in the brain. Role in cytokines-induced sickness behavior. J Neuroimmunol. 2002; 125:5–14. [PubMed: 11960635]
106. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. Nat Rev Immunol. 2007; 7:161–167. [PubMed: 17220915]
107. Perry VH, Gordon S. Macrophages and microglia in the nervous system. Trends Neurosci. 1988; 11:273–277. [PubMed: 2465626]
108. Perry VH, Matyszak MK, Fearn S. Altered antigen expression of microglia in the aged rodent CNS. Glia. 1993; 7:60–67. [PubMed: 8423063]
109. Perry VH, Newman TA, Cunningham C. The impact of systemic infection on the progression of neurodegenerative disease. Nat Rev Neurosci. 2003; 4:103–112. [PubMed: 12563281]
110. Pickering M, O'Connor JJ. Pro-inflammatory cytokines and their effects in the dentate gyrus. Prog Brain Res. 2007; 163:339–354. [PubMed: 17765728]
111. Plata-Salaman CR, Ilyin SE, Turrin NP, Gayle D, Flynn MC, Bedard T, Merali Z, Anisman H. Neither acute nor chronic exposure to a naturalistic (predator) stressor influences the interleukin-1beta system, tumor necrosis factor-alpha, transforming growth factor-beta1, and neuropeptide mRNAs in specific brain regions. Brain Res Bull. 2000; 51:187–193. [PubMed: 10709966]
112. Pocock JM, Kettenmann H. Neurotransmitter receptors on microglia. Trends Neurosci. 2007; 30:527–535. [PubMed: 17904651]
113. Poo MM. Neurotrophins as synaptic modulators. Nat Rev Neurosci. 2001; 2:24–32. [PubMed: 11253356]
114. Ransohoff RM, Perry VH. Microglial physiology: unique stimuli, specialized responses. Annu Rev Immunol. 2009; 27:119–145. [PubMed: 19302036]

115. Richwine AF, Parkin AO, Buchanan JB, Chen J, Markham JA, Juraska JM, Johnson RW. Architectural changes to CA1 pyramidal neurons in adult and aged mice after peripheral immune stimulation. Psychoneuroendocrinology. 2008; 33:1369–1377. [PubMed: 18805643]

116. Rosczyk HA, Sparkman NL, Johnson RW. Neuroinflammation and cognitive function in aged mice following minor surgery. Exp Gerontol. 2008; 43:840–846. [PubMed: 18602982]

117. Sawada M, Suzumura A, Hosoya H, Marunouchi T, Nagatsu T. Interleukin-10 inhibits both production of cytokines and expression of cytokine receptors in microglia. J Neurochem. 1999; 72:1466–1471. [PubMed: 10098850]

118. Schwartz M, Butovsky O, Bruck W, Hanisch UK. Microglial phenotype: is the commitment reversible? Trends Neurosci. 2006; 29:68–74. [PubMed: 16406093]

119. Schwartz M, Ziv Y. Immunity to self and self-maintenance: a unified theory of brain pathologies. Trends Immunol. 2008; 29:211–219. [PubMed: 18328784]

120. Sheffield LG, Berman NE. Microglial expression of MHC class II increases in normal aging of nonhuman primates. Neurobiol Aging. 1998; 19:47–55. [PubMed: 9562503]

121. Smith MA, Makino S, Kvetnansky R, Post RM. Effects of stress on neurotrophic factor expression in the rat brain. Ann N Y Acad Sci. 1995; 771:234–239. [PubMed: 8597402]

122. Soiampornkul R, Tong L, Thangnipon W, Balazs R, Cotman CW. Interleukin-1beta interferes with signal transduction induced by neurotrophin-3 in cortical neurons. Brain Res. 2008; 1188:189–197. [PubMed: 18036576]

123. Sorrells SF, Caso JR, Munhoz CD, Sapolsky RM. The stressed CNS: when glucocorticoids aggravate inflammation. Neuron. 2009; 64:33–39. [PubMed: 19840546]

124. Sorrells SF, Sapolsky RM. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav Immun. 2007; 21:259–272. [PubMed: 17194565]

125. Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. Neuroimmunomodulation. 2008; 15:323–330. [PubMed: 19047808]

126. Streit WJ. Microglia as neuroprotective, immunocompetent cells of the CNS. Glia. 2002; 40:133–139. [PubMed: 12379901]

127. Streit WJ, Miller KR, Lopes KO, Njie E. Microglial degeneration in the aging brain--bad news for neurons? Front Biosci. 2008; 13:3423–3438. [PubMed: 18508444]

128. Streit WJ, Sparks DL. Activation of microglia in the brains of humans with heart disease and hypercholesterolemic rabbits. J Mol Med. 1997; 75:130–138. [PubMed: 9083930]

129. Strle K, Zhou JH, Shen WH, Broussard SR, Johnson RW, Freund GG, Dantzer R, Kelley KW. Interleukin-10 in the brain. Crit Rev Immunol. 2001; 21:427–449. [PubMed: 11942558]

130. Sugama S, Fujita M, Hashimoto M, Conti B. Stress induced morphological microglial activation in the rodent brain: involvement of interleukin-18. Neuroscience. 2007; 146:1388–1399. [PubMed: 17433555]

131. Tapia-Arancibia L, Aliaga E, Silhol M, Arancibia S. New insights into brain BDNF function in normal aging and Alzheimer disease. Brain Res Rev. 2008; 59:201–220. [PubMed: 18708092]

132. Tian L, Rauvala H, Gahmberg CG. Neuronal regulation of immune responses in the central nervous system. Trends Immunol. 2009; 30:91–99. [PubMed: 19144568]

133. Tong L, Balazs R, Soiampornkul R, Thangnipon W, Cotman CW. Interleukin-1 beta impairs brain derived neurotrophic factor-induced signal transduction. Neurobiol Aging. 2008; 29:1380–1393. [PubMed: 17467122]

134. Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem. 2002; 9:224–237. [PubMed: 12359832]

135. Tynan RJ, Naicker S, Hinwood M, Nalivaiko E, Buller KM, Pow DV, Day TA, Walker FR. Chronic stress alters the density and morphology of microglia in a subset of stress-responsive brain regions. Brain Behav Immun. 2010; 24:1058–1068. [PubMed: 20153418]

136. Vitkovic L, Konsman JP, Bockaert J, Dantzer R, Homburger V, Jacque C. Cytokine signals propagate through the brain. Mol Psychiatry. 2000; 5:604–615. [PubMed: 11126391]

137. Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J Neurosci. 2009; 29:3974–3980. [PubMed: 19339593]

138. Walker DG, Dalsing-Hernandez JE, Campbell NA, Lue LF. Decreased expression of CD200 and CD200 receptor in Alzheimer's disease: a potential mechanism leading to chronic inflammation. Exp Neurol. 2009; 215:5–19. [PubMed: 18938162]

139. Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. J Am Geriatr Soc. 2002; 50:2041–2056. [PubMed: 12473019]

140. Wong ML, Licinio J. Localization of interleukin 1 type I receptor mRNA in rat brain. Neuroimmunomodulation. 1994; 1:110–115. [PubMed: 7489320]

141. Wright GJ, Cherwinski H, Foster-Cuevas M, Brooke G, Puklavec MJ, Bigler M, Song Y, Jenmalm M, Gorman D, McClanahan T, Liu MR, Brown MH, Sedgwick JD, Phillips JH, Barclay AN. Characterization of the CD200 receptor family in mice and humans and their interactions with CD200. J Immunol. 2003; 171:3034–3046. [PubMed: 12960329]

142. Wynne AM, Henry CJ, Huang Y, Cleland A, Godbout JP. Protracted downregulation of CX(3)CR1 on microglia of aged mice after lipopolysaccharide challenge. Brain Behav Immun. 2010; 24:1190–1210. [PubMed: 20570721]

143. Ye SM, Johnson RW. An age-related decline in interleukin-10 may contribute to the increased expression of interleukin-6 in brain of aged mice. Neuroimmunomodulation. 2001; 9:183–192. [PubMed: 11847480]

144. Ziv Y, Schwartz M. Immune-based regulation of adult neurogenesis: implications for learning and memory. Brain Behav Immun. 2008; 22:167–176. [PubMed: 17905567]

145. Zujovic V, Benavides J, Vige X, Carter C, Taupin V. Fractalkine modulates TNF-alpha secretion and neurotoxicity induced by microglial activation. Glia. 2000; 29:305–315. [PubMed: 10652441]

146. Zujovic V, Schussler N, Jourdain D, Duverger D, Taupin V. In vivo neutralization of endogenous brain fractalkine increases hippocampal TNFalpha and 8-isoprostane production induced by intracerebroventricular injection of LPS. J Neuroimmunol. 2001; 115:135–143. [PubMed: 11282163]

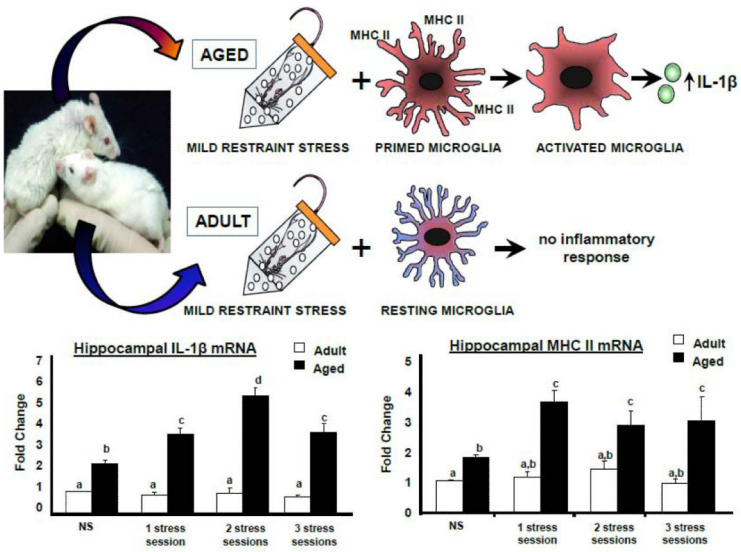

Figure 1.

A mild restraint stressor that had little or no effect on inflammation in adult mice elicited a significant neuroinflammatory response in aged mice. Aged mice not only had higher basal levels of inflammatory mediators (IL-1β, MHCII), but also showed a stress-induced increase in these inflammatory mediators, whereas expression in adult mice was unaffected by stress. Modified from (Buchanan, et al., 2008).

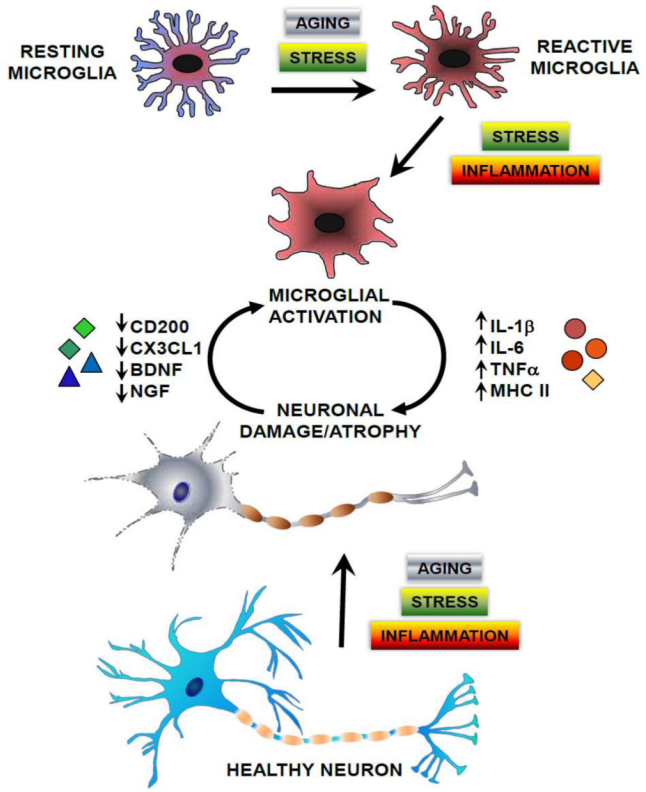

Figure 2.

Stress and aging can alter microglial reactivity leading to overactivation of microglia when additional immune challenges are applied. In addition, aging, stress and inflammation are can induce deleterious changes in neuronal structure and function leaving neurons vulnerable to inflammation-induced damage/atrophy. Excessive or prolonged inflammation (IL-1β, IL-6, TNF-α) resulting from increased microglial activation could contribute to neuronal damage as well as loss of neuroregulatory/neuroprotective mechanisms (CD200, CX3CL1, BDNF, NGF). In turn, damaged neurons would no longer adequately control microglia reactivity, thus increasing the risk of exaggerated inflammatory effects upon subsequent activation. As a result (over time), a vicious cycle of persistent microglial activation and loss of neuronal integrity could ensue, resulting in chronic neuroinflammation and prolonged neurobehavioral impairment.