Published in final edited form as:

Psychiatr Clin North Am. 2011 June ; 34(2): 437–449. doi:10.1016/j.psc.2011.02.006.

IMMUNITY, AGING, AND GERIATRIC DEPRESSION

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Abstract

Despite pioneering findings on immune functions in various depressive syndromes, few recent studies focus on the role of inflammation and its potential in generating novel antidepressant therapies. We suggest that geriatric depression is the behavioral syndrome *par excellence* in which inflammatory processes are likely to play an etiological role. We base this assertion on the following observations: Geriatric depression occurs in the context of medical and neurological illnesses in which inflammatory processes are part of their pathogenesis. Both aging and depression are associated with pronounced and prolonged immune responses. Brain areas related to mood processing, have increased inflammatory responses during aging. Moreover, the connectivity among mood regulating structures may be modulated by inflammatory responses. Geriatric depression exacerbates the pathology of its comorbid medical and neurological disorders raising the question whether depression-related inflammatory changes mediate the worsening of their outcomes. Finally, geriatric depression often occurs in persons exposed to chronic stress, a state precipitating geriatric depression and triggering pro-inflammatory responses.

The clinical lesson derived from the available information is that depressed older adults should be examined for inflammatory disorders or risk factors of inflammation. It is premature to use anti-inflammatory agents in the treatment of geriatric depression. However, treatment of co-morbid conditions increasing CNS inflammatory responses can have general health benefits and should be part of clinical practice. Neuroimaging may identify microstructural abnormalities and dysfunction of neural networks associated with inflammatory processes accompanying geriatric depression. Transgenic animal models may help to identify candidate anti-inflammatory agents that later may be tested in clinical trials of geriatric depression.

Keywords

Immunity; aging; depression; geriatrics

Introduction

The etiology of geriatric depression is not well understood. Attempts to identify etiological contributors to geriatric depression have focused on the role of its comorbid disorders and on the effects of the aging process. Geriatric depression afflicts patients with significant

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Disclosures

Dr. Morimoto: None.

Dr. Alexopoulos has received grant support by Forest Pharmaceuticals, hold equity of Johnson and Johnson, and has served in the Speakers Bureau of Forest, Astra Zeneca, Lilly, Merck, BMS, and Novartis

medical comorbidity (Alexopoulos 2005). When it occurs, depression worsens the outcomes of many medical illnesses and increases mortality. In addition to medical morbidity, geriatric depression is often accompanied by cognitive impairment. Cognitive impairment subsides, but is rarely eliminated during periods of remission (Murphy and Alexopoulos 2004). The persistence of cognitive impairment suggests that geriatric depression occurs in the context of impairment of neural structures associated with cognitive functions. The causes of impairment of these structures are variable and include vascular and neurodegenerative diseases and pronounced aging-related changes. In sum, geriatric depression occurs during broad disruption of bodily and brain functions and, when established, its pathophysiology further contributes to this disruption.

Changes in the immune system mediate disruptive processes of diseases often comorbid with geriatric depression. Inflammation is the central process underlying “sickness behavior” accompanying many of the generalized diseases including cancer, organ failure, and infections. Pro-inflammatory states resulting from immune responses to a variety of pathophysiological events contribute to central nervous system (CNS) abnormalities in neurodegenerative and cerebrovascular diseases. In particular, inflammatory processes interact with amyloid deposition and lead to pathological changes of Alzheimer’s disease (Wenk 2003; Greig, Mattson et al. 2004). Similar inflammatory responses contribute to other neurodegenerative diseases (Wang 2002). Inflammation is among the initial vascular events leading to cerebral infarction as well as part of the neuronal destruction process following cerebrovascular infarction or embolism (Ropper, Adams et al. 2005). Nonetheless, the role of inflammation in geriatric depression in patients without vascular and neurodegenerative diseases remains unclear.

Stress, a contributor to geriatric depression, leads both to behavioral and to immune changes (Frank, Baratta et al. 2007; Buchanan, Sparkman et al. 2008). Moreover, challenge of the immune system is followed by behavioral changes reminiscent of behavioral responses to stress (Hart 1988; Dantzer, O’Connor et al. 2008; Maes 2008). These findings suggest that immune changes may be at least one of the mechanisms by which stress leads to behavioral pathology.

We suggest that geriatric depression is the behavioral syndrome *par excellence* in which inflammatory processes are likely to play a central etiological role. We base this assertion on the following observations: Geriatric depression occurs in the context of medical and neurological illnesses in which inflammatory processes play a significant pathogenetic role. Both aging (Lu, Pan et al. 2004; Streit, Miller et al. 2008; Lucin and Wyss-Coray 2009) and depression (Maes 2008) are associated with pronounced and prolonged immune responses. Geriatric depression exacerbates the pathology of its comorbid medical and neurological disorders (Alexopoulos and Kelly 2009) raising the question whether depression-related inflammatory changes mediate the worsening of their outcomes. Finally geriatric depression often occurs in persons exposed to chronic adversity (stress), a state that challenges the immune system and is known to contribute to geriatric depression. Below, we describe briefly the immune functions of the CNS and summarize animal and human literature on immune changes occurring during aging and depression.

The Two Immune Systems

In humans, the immune system of the central nervous system is separate from the immune system of the periphery. However, the two immune systems interact and engage in mutual maintenance of homeostasis (Lucin and Wyss-Coray 2009). This communication serves as a “sensory pathway” through which peripheral immune stimulation informs the brain and influences behavior (Blalock 1994).

CNS Cellular Immune Component

The CNS immune system is regulated by both macroglial and microglial cells. During insult, injury, or invasion of pathogens, microglial cells are the primary first responders, becoming active before any other brain cells (Kreutzberg 1996). Microglial cells make up roughly 20% of all glia. However, in an activated state, they may encompass more surface area than astrocytes (Lawson, Perry et al. 1990; Banati and Graeber 1994).

Microglia respond to subtle alterations in their environment, and have the ability to differentiate between self/non-self when encountering molecules not present in healthy CNS such as pathogens, blood clotting factors, intracellular constituents released by necrotic cells, or immunoglobulin-antigen complexes (Hanisch and Kettenmann 2007), before pathological changes are detectable (Boya, Carbonell et al. 1987). Microglia also respond when neurons are injured as a result of trauma, infection, ischemia or neurodegeneration. During trauma, microglia become active early in the process via the release of adenosine triphosphate (ATP), neurotransmitters, cytokines, ion changes, or loss of inhibitor molecules (Hanisch and Kettenmann 2007). Their ability to respond selectively to molecules related to neurotransmission allows them to monitor their environment continuously. Therefore, the quiescent microglia phase represents a state of constant vigilance to changes in their microenvironment (Kreutzberg 1996).

Microglia show rapid morphological transformation from resting state to activated state (Gehrmann, Banati et al. 1993; Kreutzberg 1996). Microglial activation is dictated by the needs of their microenvironment and is stimulus dependent (Lucin and Wyss-Coray 2009). During the activated phase, microglia proliferate, retract their cellular processes, and increase expression of cell surface molecules. Further activation turns microglia into phagocytes, which are phenotypically and morphologically indistinguishable from macrophages in the periphery. These “brain macrophages” secrete cytokines, growth factors, oxygen and nitrogen free radicals, neurotransmitters and proteolytic enzymes (Giulian, Baker et al. 1986; Gehrmann, Banati et al. 1993; Banati and Graeber 1994; Jones 2008). Through the release of these mediators, microglia influence the differentiation and survival of other CNS cells such as neurons, astrocytes, and oligodendrocytes (Jones 2008). Activated microglia also produce Trk A, Trk B, and Trk C receptors, and respond to and produce brain-derived neurotrophic factor (BDNF) (Nakajima, Kikuchi et al. 1998).

Astrocytes, recruited by microglia, are part of the CNS immune response (Blasko, Stampfer-Kountchev et al. 2004). Once activated, astrocytes metabolize extracellular neurotransmitters, produce extracellular matrix molecules (ECM) and provide neurotrophic support to damaged neurons (Darlington 2005). Like microglia, astrocytes produce cytokines and chemokines. They also play a role in the synthesis of ECM molecules by microglia. Subsequently, ECM molecules may stimulate production of cytokines and growth factors by microglia that trigger astroglial proliferation (Darlington 2005).

The activation of microglia can be both neuroprotective and neurotoxic (Kreutzberg 1996). Microglia facilitate the return to homeostasis after neurophysiologic insult by participating in tissue repair after injury, removing cytokines and invading microorganisms, and by secreting wound healing factors. However, excessive or prolonged activation of microglia can be cytotoxic through the release of excitatory amino acids, quinolinic acid and cytokines (Dilger and Johnson 2008).

CNS Humoral Immune Component

Cytokines are a diverse group of polypeptides associated with immune cell function and chemotaxis in both the CNS and the periphery (Wang 2002). Virtually all cells in the CNS

have been shown to produce and respond to a range of cytokines (Jones 2008), though under normal conditions, cytokine production in the CNS is low to undetectable (Wang 2002). Cytokines play a critical role in maintaining homeostasis through the removal of damaged cells, clearing of infections as well as tissue repair and neuroregeneration. However, depending on the magnitude, length and timing of their induction, cytokine cascades are capable of exacting severe tissue damage and have been implicated in the pathogenesis of a range of neurodegenerative disorders, stroke, and multiple sclerosis (Wang 2002).

Periphery – Brain Immune Communication

Following exposure to pathogens, the non-specific immune response begins rapidly with the activation of neutrophils and macrophages in the periphery. These cells engulf and destroy pathological agents and also release cytokines. Cytokines, then recruit additional immune cells to the site of infection or injury. They also initiate the peripheral acute-phase response to fight infection and repair the host tissue. The stimulated peripheral immune system may progress to an antigen-specific, adaptive, immune response by recruiting T and B lymphocytes. Once the invading pathogen has been neutralized, the peripheral immune system returns to a quiescent state so that it minimizes damage to tissue by the inflammatory response. Communication between the peripheral immune system and the brain initiates immunologic, physiologic and behavioral responses to insult or infection (Godbout and Johnson 2006).

The brain receives information from the periphery about the immune status of the organism and, in turn, may change the organism's behavior. Inflammatory cytokines communicate the immune status of the periphery to the CNS through the following mechanisms: *1. Active transport:* Certain cytokines (IL-1 beta, IL-6, TNF α , and IL 1 alpha) cross the blood brain barrier through a saturable transport system (Banks 2001). *2. Crossing at circumventricular organs:* Cytokines may enter the CNS in the areas of the circumventricular organs where the blood brain barrier is more permeable or absent. *3. Humoral route:* Cytokines may bind to receptors within cerebral blood vessels and induce the production of second messengers that then, diffuse into the brain and alter neural activity (Maier and Watkins 2003). *4. Neural route:* Peripheral cytokines may directly stimulate vagal and trigeminal afferents fibers, which can carry visceral sensory information to the CNS (Maier, Goehler et al. 1998; Goehler, Gaykema et al. 2000; Romeo, Tio et al. 2001). Activation of the neural pathway sensitizes target brain structures for the production and action of cytokines that may diffuse from the circumventricular organs and the choroid plexus into the brain. The periphery-CNS immune communication is redundant (Godbout and Johnson 2006). The afferent neural pathways are quicker and more direct than other forms of transport. However, all forms of communication rely on the production of pro-inflammatory cytokines by microglial cells in the brain (Dilger and Johnson 2008).

Aging, CNS Immunity and Behavior

Aging increases the brain's inflammatory responses. With aging there is an increase in glia activation, inflammatory mediators, and atrophy (Lu, Pan et al. 2004; Streit, Miller et al. 2008; Lucin and Wyss-Coray 2009). Both human and animal studies show that genes related to cellular stress, and inflammation are upregulated with age, while genes related to synaptic function, growth factors and trophic support are down-regulated (Lee, Weindruch et al. 2000; Lu, Pan et al. 2004; Lucin and Wyss-Coray 2009). Neurogenesis also decreases with age, in part, due to the effects of cytokines secreted by activated microglia (Carpentier and Palmer 2009).

A combination of both senescence of microglia and increased secretion of inflammatory proteins may contribute to the pro-inflammatory shift during aging. Activation of microglia

places a burden on the cells' metabolic mechanisms, which can only tolerate high levels of activity for short time periods (Streit, Miller et al. 2008). Activated microglia are prone to die more often and more quickly than non-activated microglia (Streit, Miller et al. 2008). Microglial losses are replenished by mitosis of parenchymal microglia, or by migration of bone marrow progenitor cells. Both processes are enhanced during times of injury or inflammation (Graeber, Tetzlaff et al. 1988; Flugel, Bradl et al. 2001). The mitotic potential of microglia, is not reduced, and perhaps is even enhanced in old age (Conde and Streit 2006). Therefore, increased mitosis, coupled with increased activation, may promote production of senescent microglia (Streit, Miller et al. 2008).

"Dystrophic" microglia may increase in the aging brain. These microglia are characterized by abnormalities in cytoplasmic structure such as deramified, atrophic or fragmented processes (Streit, Miller et al. 2008). Dystrophic microglia secrete diminished levels of neurotrophic factors and have limited phagocytic function. The combination of diminished neurotrophic factors and downregulated phagocytosis, with increased secretion of inflammatory mediators may lead to both neuron loss, and inefficient clearance of toxic substances associated with neurodegenerative disease (Lucin and Wyss-Coray 2009).

Along with immune cellular changes, aging attenuates the ability of the peripheral immune system to initiate an effective immune response (Gruver, Hudson et al. 2007) and increases the innate immune activity (Dantzer, O'Connor et al. 2008; Dilger and Johnson 2008). These changes result in increased peripheral immune stimulation and, through periphery-CNS communication, to increased production of inflammatory markers in the CNS (Wei, Xu et al. 1992; Ershler, Sun et al. 1993; Hager, Machein et al. 1994; Godbout and Johnson 2006).

In addition to influencing central and peripheral immune responses, aging disrupts communication between the periphery and the CNS. Peripheral immune stimulation in healthy older subjects produces both an increased and discordant CNS inflammatory response compared with younger subjects (Godbout and Johnson 2006; Dilger and Johnson 2008). Increased immune reactivity, combined with exaggerated CNS immune response to stimulus may leave some older adults in a chronic state of neuroinflammation characterized by continuous production of pro-inflammatory cytokines (Ye and Johnson 1999; Dilger and Johnson 2008). Therefore, aging renders microglia hypervigilant, and prone to excessive and prolonged release of cytokines when challenged by immune stimuli (Wei, Xu et al. 1992; Ershler 1993; Ershler, Sun et al. 1993; Hager, Machein et al. 1994; Maggio, Guralnik et al. 2006).

In aged mice, lipopolysaccharide injections caused both exaggerated neuroinflammatory response and prolonged "sickness behavior" compared to younger adult mice (Godbout, Chen et al. 2005). In these mice, sickness behavior lasted almost twice as long as in younger mice and was associated with a pronounced induction of peripheral and brain indoleamine 2,3-dioxygenase (IDO) and a much higher rate of turnover in brain serotonin (Godbout, Chen et al. 2005). Discordant central inflammatory response to peripheral stimulation can have damaging effects to an organism due to the behavioral effects and neurotoxicity associated with the disproportionate release of pro-inflammatory cytokines in the brain (Dilger and Johnson 2008).

Immune Changes in Geriatric Depression

Limited information exists on the role of the immune system in geriatric depression. Most findings are derived from aging animal experiments, on models of stress and depression, and on sparse clinical studies.

Pro-inflammatory cytokines exert profound effects on behavior. The set of behaviors occurring after insult or infection has been collectively referred to as “sickness behavior” (Hart 1988; Dantzer, O’Connor et al. 2008). Behavioral symptoms include reduced food and water intake, decreased exploration, decreased social interaction, increased somnolence, as well as changes in both mood and cognition (Dantzer, O’Connor et al. 2008; Sparkman and Johnson 2008). In humans, “sickness behavior” shares many symptoms and signs with major depression. This resemblance led to the suggestion that depression is a behavioral response to pro-inflammatory changes (Maes 2008).

The complexity of “sickness behavior” suggests that it is mediated by neural systems including structures mediating the depressive syndrome. As an example, IL-1, a pro-inflammatory cytokine, has receptors in the granule cell layer of the dentate gyrus, the pyramidal cell layer of the hippocampus, the anterior pituitary gland (Parnet, Kelley et al. 2002), and the endothelial cells of the brain venules. High densities of IL-1 receptors were found in the preoptic and supraoptic areas of the hypothalamus and the subfornical organ, and lower densities in the paraventricular hypothalamus, cortex, nucleus of the solitary tract and the ventrolateral medulla (Konsman, Vignes et al. 2004). It is important to note, that cytokines do not only affect neurons, but also modulate the function of both endothelial and glial cells (Dantzer, O’Connor et al. 2008).

Aging increases inflammatory responses in distinct brain areas. In old rodents, glia cultures and brain sections, including those of areas related to mood processing, had greater increases in IL-6, IL-1 β and TNF α compared to younger animals after challenge with lipopolysaccharide (Ye and Johnson 1999; Terao, Apte-Deshpande et al. 2002). Coronal sections of the cerebral cortex of aged mice spontaneously produce higher levels of IL-6 than do sections from adult animals (Ye and Johnson 2001; Xie, Morgan et al. 2003). IL-6 is not only elevated in the whole brain of older animals, but concentrated in the hippocampus, cerebral cortex and cerebellum compared with younger cohorts (Ye and Johnson 1999; Ye and Johnson 2001). Taken together, these observations suggest that aging of the brain’s inflammatory responses may lead to abnormalities in neural systems related to the development of depressive syndromes.

Geriatric depression is often accompanied by cognitive dysfunction. It is noteworthy that, although cytokine receptors are spread throughout the CNS, the highest levels of cytokine binding occurs in areas related to both learning and memory, including the hippocampus (Parnet, Kelley et al. 2002). Increased levels of IL-1 β have been shown to disrupt long term potentiation (LTP), a cellular mechanism important in the consolidation of memory. In animals, injection of IL-1 β can impair hippocampal dependent memory performance (Rachal Pugh, Fleshner et al. 2001). In addition, behavioral performance on tests of spatial learning memory can be disrupted by infection or peripheral immune activation and the resultant cytokine up-regulation (Barrientos, Higgins et al. 2006; Sparkman, Buchanan et al. 2006).

Exposure to stress not only serves as a precipitating factor of depressive episodes in late life but also promotes inflammation and influences cognitive functions and behavior. Chronic stress enhances the aging related pro-inflammatory state by activating microglia and up-regulating the expression of cell surface antigens (Frank, Baratta et al. 2007; Buchanan, Sparkman et al. 2008). Earlier exposure to a particular stressor can prime microglia and increase its inflammatory response (Johnson, O’Connor et al. 2002; Frank, Baratta et al. 2007). Mild stress increases cytokine production, and decreases learning and memory functions in aged and adult mice. However, if stressors are repeated over a number of days, only aged animals continue to show cognitive impairment, whereas adult mice return to baseline performance. Stress-induced IL-1 β production was found only in aged animals;

infusions of IL-1 receptor antagonists (IL1RA) appear to lessen the negative consequences of IL-1 β on learning and memory. Similarly, external stressors increased circulating IL-1 β and IL-6 and promoted cognitive impairment in older adults (Sparkman and Johnson 2008). Patients treated with the innate immune cytokine IFN- α exhibited greater activation of the dorsal anterior cingulate than controls (Capuron, Pagnoni et al. 2005); abnormalities of the anterior cingulate have been documented in geriatric depression and found to be associated with poor antidepressant response (Alexopoulos, Kiessses et al. 2002; Alexopoulos, Murphy et al. 2007; Alexopoulos, Murphy et al. 2008).

The inflammatory response to immune challenge influences neural systems responsible for mood regulation. In humans, typhoid injection produced an inflammatory response evidenced by increased circulating IL-6 and development of sad mood. Worsening of mood during inflammatory responses correlated with enhanced activity within the subgenual anterior cingulate cortex (ACC) during processing of emotional stimuli (Harrison, Brydon et al. 2009). The subgenual cingulate is a central node of the emotional control system, which often dysfunctions in depression. Inflammation-associated mood change reduces connectivity of the subgenual ACC to amygdala, medial prefrontal cortex, nucleus accumbens, and superior temporal sulcus, and is modulated by peripheral IL-6 (Harrison, Brydon et al. 2009). In addition, a single nucleotide polymorphism (SNP) of the gene encoding the inflammatory cytokine IL-1 β has been associated with both reduced activity of the anterior cingulate and the amygdala in response to emotional stimuli and with non-remission of major depression following antidepressant treatment (Baune, Dannlowski et al.). These findings raise the question whether inflammatory processes participate in the mechanisms mediating the development of depressive and cognitive symptoms in late life especially during exposure to chronic stress.

Studies of older depressed patients or elders at risk for depression documented abnormalities in inflammatory responses. A recent meta-analysis showed that depressed patients have higher concentrations of IL-6 and TNF α compared to control subjects (Dowlati, Herrmann et al.). Epidemiologic studies found an association of elevated IL-6 with depressive symptoms after controlling for likely confounding variables (Dentino, Pieper et al. 1999; Penninx, Kritchewsky et al. 2003; Tiemeier, Hofman et al. 2003; Bremner, Beekman et al. 2008). In geriatric depressed patients, peripheral inflammatory markers were correlated with the severity of depressive symptoms overall (Diniz, Teixeira et al.; Diniz, Teixeira et al.; Thomas, Davis et al. 2005; Grassi-Oliveira, Brietzke et al. 2009) as well as with cognitive symptoms of depression. (Gimeno, Kivimaki et al. 2009). IL-6 was associated with increased suicide risk, with the highest levels of IL-6 correlating with the most violent suicide attempts (Lindqvist, Janelidze et al. 2009). In addition, inflammatory markers predicted depressive symptoms in older adults during three and six year follow-ups (Milaneschi, Corsi et al. 2009). Caregiving for an ill relative also increases both depressive symptoms and inflammatory markers in the elderly. In cross-sectional studies, family caregivers of dementia patients had higher levels of circulating IL-6 levels than age-matched controls (Lutgendorf, Garand et al. 1999). Other studies have indicated that, not only are circulating cytokine levels higher, but the response to immune challenge lasts longer in stressed elderly populations. Specifically, elderly caregivers had a prolonged elevation in IL-6 of up to four weeks following influenza vaccine, where as there was no IL-6 change in non-caregiving age matched controls (Harris, Ferrucci et al. 1999). Finally, in addition to depressed mood, increased inflammatory indices are associated with development of cognitive impairment, disability and mortality in late life (Ferrucci, Harris et al. 1999; Harris, Ferrucci et al. 1999; Weaver, Huang et al. 2002; Maggio, Guralnik et al. 2006).

Pharmacological studies provide indirect evidence in support of the inflammation hypothesis of depression. While definitive studies are lacking, there is early evidence that classical

antidepressants may influence inflammatory processes and conversely anti-inflammatory agents may have antidepressant action. Animal studies have shown that tricyclic antidepressants reduce pro-inflammatory and increase anti-inflammatory cytokines (Kubera, Kenis et al. 2000; Kubera, Kenis et al. 2000; Kubera, Kenis et al. 2001). Some antidepressants ameliorate "sickness behavior" and reduce production of cytokines in animal models of inflammation (Yirmiya, Tio et al. 1996). Select antidepressants may reduce serum cytokines (Maes, Song et al. 1999; Lin, Song et al. 2000; Szuster-Ciesielska, Tustanowska-Stachura et al. 2003), although this finding needs to be confirmed. Pre-treatment cytokine plasma levels may influence the response to antidepressants (O'Brien, Scully et al. 2007; Eller, Vasar et al. 2008). Moreover, there is anecdotal evidence that the anti-inflammatory agent minocycline augments the action of some antidepressants in major depression (Pae, Marks et al. 2008). Similarly, the cyclo-oxygenase-2 inhibitor celecoxib may augment the efficacy of reboxetine, and fluoxetine in major depression (Muller, Schwarz et al. 2006; Akhondzadeh, Jafari et al. 2009). Finally, the anti-inflammatory agent etanercept reduced symptoms of depression in patients with psoriasis (Tyring, Gottlieb et al. 2006).

Transgenic Animals

Several transgenic inflammatory animal models have been developed and can be used to test the relationship of inflammatory responses to depression-like behavior. What follows is a selective summary of some such models.

The GFAP-IL6 transgenic mouse presents an up-regulation of IL-1 α/β and TNF α as well as gliosis of both astrocytes and microglia in the cerebellum, brain stem and sub-cortical regions (Chiang, Stalder et al. 1994). Functional deficits in this mouse include various learning impairments, decreased locomotor and exploratory behavior, reduced long-term potentiation in hippocampal slices, and abnormal hypothalamic-pituitary-adrenal axis responses to immobilization stress. In contrast, IL-6 deficient mice are less sensitive to the behavioral effects of IL-1 β or to lipopolysaccharide injected centrally or peripherally. For example, IL-6 knock-out mice are resistant to lipopolysaccharide induced deficits in spatial working memory. These mice still show an increase in plasma TNF α and IL-1 β when immune challenged, but do not show the working memory deficits that the knock-in mice show. In this sample, working memory performance was associated with reduction in TNF α and IL-1 β production in the neuronal cell layer of the hippocampus in the IL-6 knock-out mice (Sparkman, Buchanan et al. 2006).

Type 1 IL-1 receptor knock-out mice do not respond to the administration of IL-1 but do show behavioral changes in response to lipopolysaccharide injection, perhaps mediated by the pro-inflammatory cytokine TNF α . This observation indicates that the reduction of expression of one cytokine can be replaced by the actions of a complementary cytokine mediator. However, blockade of IL-1 action through the administration of IL-1RA (receptor antagonist) reduces sickness behavior, part of which is a reduction of social exploration (Konsman, Tridon et al. 2000) and food intake, suggesting that IL-1 may be a critical mediator of sickness behavior (Konsman, Tridon et al. 2000; Dantzer, O'Connor et al. 2008).

The knock-out mouse of the anti-inflammatory cytokine IL-10 respond to lipopolysaccharide injection with exaggerated and prolonged sickness behavior and an increase in CNS pro-inflammatory cytokines (Dantzer, O'Connor et al. 2008). Aging reduces IL-10 production. Therefore, aging related reduction of IL-10 may be one of the mechanisms promoting the pro-inflammatory state of late life.

Conclusion

Aging disrupts peripheral and CNS immune responses and influences communication between the periphery and the CNS. Consequently, immune stimulation produces both exaggerated and discordant CNS inflammatory responses in older adults. The net result of these changes is a pro-inflammatory state characterized by senescence of microglia and increased secretion of inflammatory proteins.

Aging may exacerbate the effects of stress in the CNS leading to behavioral and cognitive changes similar to those of the depressive syndrome. Chronic stress exacerbates age-related increases in inflammation. Moreover, earlier exposure to a particular stressor can prime microglia and increase its inflammatory responses.

Sparse direct information exists on the role of inflammation in geriatric depression. Pro-inflammatory proteins have profound behavioral effects. "Sickness behavior", the behavioral syndrome caused by brain inflammatory processes resembles the depressive syndrome and often occurs in disorders co-morbid with geriatric depression. The complexity of "sickness behavior" suggests that it is mediated by neural systems distributed throughout brain and includes networks responsible for mood regulation. Indeed, animal studies suggest that brain areas related to mood processing, have increased inflammatory responses during aging. Moreover, the connectivity among mood regulating structures may be modulated by inflammatory responses.

Some inflammatory markers have been found elevated in geriatric depression and their levels are correlated with the severity of the syndrome. Furthermore, peripheral cytokine levels were associated with suicide risk. In addition to depressed mood, increased inflammatory indices may be associated with development of cognitive impairment, disability and mortality in late life. Conditions increasing the risk for depression, such as caregiving, may increase both depressive symptoms and inflammatory markers in the elderly.

The role of inflammation in geriatric depression needs further investigation. The clinical lesson derived from the available information is that depressed older adults should be examined with the goal to identify disorders or risk factors with known associations to inflammation. Autoimmune disorders and vascular risk factors such as hyperlipidemia and increased C-reactive protein are examples of such conditions. It is premature to use anti-inflammatory agents in the treatment of the depression syndrome of older adults. However, treatment of co-morbid conditions increasing CNS inflammatory responses can have general health benefits and should be part of clinical practice.

Neuroimaging and electrophysiological studies may identify microstructural abnormalities and disturbances in activation and function of neural networks associated with the inflammatory processes accompanying geriatric depression. Transgenic animal models may help to identify candidate anti-inflammatory agents that later may be tested in clinical trials of geriatric depression.

Acknowledgments

This work was supported by NIMH grants T32 MH19132, R01 MH079414, and P30 MH085943 to Dr. Alexopoulos

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