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THE INFLAMMATION HYPOTHESIS IN GERIATRIC DEPRESSION

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Abstract

Background—A large body of research has focused on "mediating mechanisms" and predisposing brain abnormalities to geriatric depression, but little is known about its etiology. This paper examines whether age-related and comorbid disease-related immune deregulation is an etiologic contributor to geriatric depression.

Methods—This article reviews findings on neuroinflammation during the aging process and depression as well as studies of anti-inflammatory actions of classical antidepressants and antidepressant actions of anti-inflammatory agents.

Results—Aging results in increased peripheral immune responses, impaired peripheral-CNS immune communication, and a shift of the CNS into a pro-inflammatory state. These exaggerated and prolonged immune responses may lead to changes in the function of emotional and cognitive networks pertinent to geriatric depression and to behavioral changes reminiscent of the depressive and cognitive symptoms of geriatric depression. Some antidepressants may reduce the expression of inflammation markers. Limited data suggest that some anti-inflammatory agents may have antidepressant properties.

Conclusions—A synthesis of available findings suggests that aging-related and comorbid disease-related inflammatory processes may promote changes in the neural systems predisposing to geriatric depression or facilitating metabolic changes that mediate depressive syndromes. The "inflammation hypothesis" in geriatric depression cannot be tested in its entirety, but it can lead to testable hypotheses and data on mechanisms by which inflammatory processes promote geriatric depression. The significance of such an effort is that it may lead to a novel treatment development model bringing to bear recent advances of anti-inflammatory pharmacology to the treatment of depressed elderly patients.

Keywords

Immunity; aging; depression; geriatrics

INTRODUCTION

A model intended to organize research in geriatric depression proposed that factors contributing to this disorder be divided into "mediating mechanisms", "predisposing brain abnormalities" and "etiological contributors"(Alexopoulos 2005). According to this model the symptoms and signs of geriatric depression are mediated by metabolic brain changes;

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hypometabolism in several dorsal neocortical structures and hypermatabolism in some ventral limbic structures (Alexopoulos 2002). These metabolic changes are more likely to develop in predisposed persons with abnormalities in brain structures responsible for emotional regulation including those of the cognitive control (dorsal anterior cingulate and the lateral prefrontal cortex), the emotional control system (dorsal and rostral anterior cingulate and amygdala), and the hippocampus. Aging and disease-related processes may serve as etiological factors by either directly promoting metabolic changes mediating the depressive syndrome, or by increasing brain abnormalities predisposing to geriatric depression. In addition, chronic stress may lead to depression by promoting abnormal processes at each of the three levels, i.e. mediating mechanisms, predisposing abnormalities, and etiological contributors. A large body of research has focused on mediating mechanisms and predisposing brain abnormalities (emotional and cognitive control systems) to geriatric depression but much less attention has been given to their etiology.

Abnormal immune responses have been hypothesized to contribute to development of depressive symptoms and signs (Maes 2010). Despite encouraging findings, the immune hypothesis of depression has led to few attempts at novel antidepressant treatment development. This paper reviews findings on the effects of both aging and aging-related processes on CNS immunity with the goal of examining whether inflammatory processes are likely contributors to brain changes predisposing to depression or mediating geriatric depression syndromes.

CNS IMMUNE REGULATION

Historically, the CNS has been considered an immune-privileged organ, as it lacks a lymphatic system and is somewhat shielded from the circulatory system by the blood-brain barrier(Lucin and Wyss-Coray 2009; Yang, et al.). However, it is now understood that the CNS has its own immune system that is distinct from but interacts with the immune system of the periphery. Communication of peripheral immune responses to the CNS leads to changes in both the CNS immune responses and in behavior (Blalock 1994).

The CNS immune system is regulated by both macroglial and microglial cells. The first line of CNS immune defense are microglia (Kreutzberg 1996), comprising 5% to 20% of the total CNS glial cell population. Most of the time, microglia exist in a quiescent phase (Kreutzberg 1996). However, some microglia reside in a “primed” state characterized by shortened processes, and expression of cell surface markers. These microglia are similar to activated microglia but do not secrete significant cytokines. However, primed microglia can be rapidly induced and lead to greater cytokine production than non-primed microglia. Stimulation with an antigen activates microglia and leads to retraction of cellular processes, changes in surface marker expression, and the release of cytokines. Further activation turns microglia into phagocytes, similar to macrophages in the periphery. Activated microglia secrete cytokines, growth factors, oxygen and nitrogen free radicals, neurotransmitters and proteolytic enzymes (Banati and Graeber 1994; Gehrmann, et al. 1993; Giulian, et al. 1986; Jones, et al. 2008). Microglia recruit and activate astrocytes (Blasko, et al. 2004), which also produce cytokines and chemokines, metabolize extracellular neurotransmitters, and support damaged neurons through neurotrophic substances (Darlington 2005). The activation of microglia can be both neuroprotective and neurotoxic (Kreutzberg 1996). Microglia facilitate the return to homeostasis once an insult is contained by participating in tissue repair, by removing offending agents and cytokines, and by secreting injury healing factors. However, excessive activation of microglia can be cytotoxic through the release of excitatory amino acids and cytokines (Dilger and Johnson 2008).

Cytokines are polypeptides central to the function of both the CNS and the peripheral immune system(Wang 2002). In the CNS, they are mainly produced by microglia and astroglia though all CNS cells are capable of cytokine production (Wang 2002). Cytokines can be broadly grouped into related families including tumor necrosis factor (TNF), interleukin (IL), interferon (INF), colony stimulating factor (CSF) and transforming growth factor (TGF) (Wang 2002). Cytokines are part of the homeostatic apparatus, able to participate in removal of damaged cells as well as in repair and neuroregeneration processes. However, depending on the magnitude, length and timing of their induction, cytokines can exact severe tissue damage and have been implicated in some neurodegenerative and immune disorders as well as in stroke (Wang 2002).

Cytokines play a central role in the system by which the peripheral immune system communicates with the CNS (Dilger and Johnson 2008). They may enter the CNS through areas of blood brain barrier that are highly permeable or through active transport (Banks 2001). Cytokines may also bind to receptors within cerebral blood vessels and induce the production of second messengers that, then, diffuse into the brain (Maier and Watkins 2003). Finally, peripheral cytokines may directly stimulate vagal and trigeminal afferent fibers and trigger production of cytokines in the CNS (Goehler, et al. 2000; Maier, et al. 1998; Romeo, et al. 2001).

AGING OF CNS IMMUNITY

The aging process shifts the organism into a pro-inflammatory state. This shift is mediated by increased immune responses in the periphery, disruption of the periphery-CNS immune communication, and an increased and discordant CNS response. More than half of the genes upregulated during late life are genes regulating inflammatory processes (Lee, et al. 2000; Lu, et al. 2004; Lucin and Wyss-Coray 2009).

Aging disrupts the peripheral immune system leading to excessive innate immune activity (Gruver, et al. 2007). Disruption in the periphery-CNS immune communication further contributes to a pro-inflammatory shift of CNS. As a consequence, peripheral immune stimulation produces a disproportional CNS inflammatory response in older adults, leaving some older adults in a chronic state of neuroinflammation characterized by continuous production of pro-inflammatory cytokines (Dilger and Johnson 2008; Ye and Johnson 1999).

The pro-inflammatory shift of the aging CNS is characterized by increased numbers of both activated and primed microglia, continuous production of pro-inflammatory cytokines, and decreases in anti-inflammatory molecules (Sparkman and Johnson 2008). Dystrophic changes in microglia result in morphological changes including atrophic or fragmented processes, diminished phagocytic function, reduced ability to secrete neurotrophic factors, and increased production of inflammatory proteins (Streit, et al. 2008). Activated microglia have a shorter life span than quiescent microglia (Streit et al. 2008) but are replenished by mitosis of parenchymal microglia, or by migration of bone marrow progenitor cells during injury or inflammation (Flugel, et al. 2001; Graeber, et al. 1988). Interestingly, the mitotic ability of microglia, is not reduced, and may even be enhanced in late life (Conde and Streit 2006). However, increased mitosis, along with increased activation, may promote further production of senescent microglia (Streit et al. 2008).

In summary, aging renders microglia hypervigilant, and prone to excessive and prolonged release of cytokines IL-1β, IL-6 and TNF-α when challenged by immune stimuli (Ershler 1993; Ershler, et al. 1993; Godbout and Johnson 2006; Hager, et al. 1994; Maggio, et al. 2006; Wei, et al. 1992). Activation of microglia places a burden on the cells metabolic mechanisms. The end results of these processes are neuron loss, inefficient clearance of

neurotoxic molecules, and reduction of neurogenesis (Carpentier and Palmer 2009; Lucin and Wyss-Coray 2009).

INFLAMMATORY INDICES IN GERIATRIC DEPRESSION

The relationship between immune, endocrine and neurotransmitter functions generated interest in the role of immune regulation in the pathogenesis of depression. In his ground breaking work, Maes and his co-workers suggested that depression is characterized by cell-mediated immune activation (Maes 1993; Maes, et al. 1990; Maes, et al. 1993) Support for this hypothesis was provided by increases in the numbers and percentages of T cells with activation markers, enhanced stimulated production of INF-γ, higher neopterin and soluble TNF receptor-1 or 2 levels, induction of indoleamine 2,3 deoxygenase (IDO), and glucocorticoid resistance in immune cells (Maes 2010). Additional markers of immune activation have also been identified in depression. These include increased numbers of neutrophils and monocytes, increased prostaglandin E2, haptoglobin, and C-reactive protein (CRP) in the peripheral blood of depressed patients (Calabrese, et al. 1986; Joyce, et al. 1992; Maes, et al. 1997; Sluzewska, et al. 1996).

Peripheral cytokines have been studied in younger adult major depression. A meta-analysis of community and clinical samples found evidence that serum levels of IL-6, IL-1, IL-1ra and CRP are associated with depressive symptoms (Howren, et al. 2009). The associations between cytokines and depression were stronger in clinical samples with high severity of depression than community samples suggesting a “dose-effect relationship”. A more recent meta-analysis evaluated findings of 24 studies of unstimulated levels of cytokines in patients with major depression (Dowlati, et al.). This study concluded that there are significantly higher concentrations of IL-6 and TNF-α in depressed compared to control subjects, but either no evidence or inconclusive evidence of differences in IL-1β, IL-4, IL-2, IL-8, IL-6, IL-10, and INF-γ.

Peripheral cytokines levels have also been investigated in both older depressed and older community residents. The rationale of these studies has been that pro-inflammatory cytokines can contribute to the development of depressive symptoms and induce stress-reactive hormonal and brain neurotransmitter changes similar to those of depression.

There have been five epidemiologic studies focused on the relationship of peripheral cytokines to depressive symptoms in older adults (Bremmer, et al. 2008; Dentino, et al. 1999; Milaneschi, et al. 2009; Penninx, et al. 2003; Tiemeier, et al. 2003). The most consistent finding has been an association of elevated IL-6 with depressive symptoms after controlling for likely confounding variables (Bremmer et al. 2008; Dentino et al. 1999; Penninx et al. 2003; Tiemeier et al. 2003). In the Health, Aging and Body Composition sample, the association between IL-6 serum level and depressive symptoms was stronger in older men than in older women (Penninx et al. 2003). In the Rotterdam Study sample, high IL-6 levels were found in older adults with depressive disorders with similar IL-6 serum levels among those with dysthymia, minor or major depression (Tiemeier et al. 2003). The association of IL-6 elevation with major depression was confirmed by the Longitudinal Aging Study Amsterdam (LASA) (Bremmer et al. 2008). Finally, the InCHIANTI study observed an elevation of IL-1ra in older adults with depressive symptoms. Moreover, high IL-1ra levels were a risk factor for developing depressive symptoms during a 6 year follow-up (Milaneschi et al. 2009).

Studies of patients with depressive disorders indicate elevated IL-1β levels in geriatric major depression although some disagreement exists. An early study found no significant differences in peripheral IL-1β, IL-6 and TNF-α between older women with major depression and normal female controls (Brambilla and Maggioni 1998). However, a well

designed study observed that older adults with major depression, but not those with subsyndromal depression, had higher IL-1β serum levels than similarly aged controls (Thomas, et al. 2005). A functional polymorphism in the promoter region of the IL-1β gene (IL-1β-511c/t) is associated with age of early onset of geriatric depression (Diniz, et al. 2010a). IL-1β was correlated with severity of depression (Thomas et al. 2005). In other studies of depressed elderly patients, several inflammatory markers (plasma: TNF-α, IL-6 and IL-1β) were correlated with the severity of depressive symptoms overall (Diniz et al. 2010a; Diniz, et al. 2010b; Grassi-Oliveira, et al. 2009; Thomas et al. 2005) as well as cognitive symptoms of depression (Gimeno, et al. 2009). In addition, IL-6 is associated with increased suicide risk, with the highest levels of IL-6 correlating with the most violent suicide attempts (Lindqvist, et al. 2009).

Peripheral cytokines have been found to be elevated in older adults at risk for depression. Caregiving for an ill relative 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 than age-matched controls (Lutgendorf, et al. 1999). 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, et al. 1999).

Circulating inflammatory cytokines are elevated in conditions comorbid with geriatric depression. Serum levels of IL-1 have been correlated with various aspects of cardiovascular disease and its outcomes (Apostolakis, et al. 2008). In vitro studies have demonstrated that IL-1a, IL-1b, and IL-18 have atherogenic properties including up-regulation of adhesion molecules, activation of macrophages, and smooth muscle proliferation (Apostolakis et al. 2008). Other cytokines have been implicated as well. In the sample of the Health, Aging and Body Composition Study, increased IL-6 and TNF-α levels in the periphery were a risk factor of subclinical and clinical cardiovascular disease (Cesari, et al. 2003). These findings have been confirmed by others (Kritchevsky, et al. 2005). IL-6 and TNF-α are both acute-phase proteins. In the periphery, IL-6 is secreted by macrophages and monocytes and leads to proliferation of B cells (Hodgkin, et al. 1988; Mayer, et al. 1991). TNF-α is secreted by macrophages, mast cells, and natural killer cells and is associated with release of pro-inflammatory cytokines and prostaglandins from macrophages (Lindemann 1991). Finally, increased inflammatory indices (plasma IL-6) are associated with development of cognitive impairment, disability and mortality in late life (Ferrucci, et al. 1999; Harris et al. 1999; Maggio et al. 2006; Roubenoff, et al. 2003; Weaver, et al. 2002).

Stress, a precipitant of depression, promotes inflammation in both aged animals and humans. Stress can activate microglia and upregulate the expression of cell surface antigens such as major histocompatability complex (MHC) class II (Frank, et al. 2007). Chronic stress further exacerbates age-related increases in inflammation (Buchanan, et al. 2008). In addition, earlier exposure to a particular stressor can prime microglia and increase its inflammatory responses to subsequent encounters with that stressor (Frank et al. 2007; Johnson, et al. 2002). External stressors have been associated with increases in circulating IL-1β and IL-6 and in cognitive impairment in elderly patients (Sparkman and Johnson 2008).

Most of the evidence linking inflammation to geriatric depression with inflammation is based on measures of peripheral inflammatory markers. It is difficult for these large molecules to cross the blood brain barrier. Peripheral immune responses may be followed by CNS immune changes through the periphery-CNS communication system. Thus, a pro-inflammatory state of the periphery can serve as a stimulus for direct studies of the CNS

inflammatory status in geriatric depression. Such studies are feasible in humans because several PET ligands are now available permitting *in vivo* assessment of activated microglia.

PUTATIVE IMMUNE MECHANISMS IN GERIATRIC DEPRESSION

Several mechanisms may explain the relationship of pro-inflammatory cytokines to depression. High plasma IL-6 levels were associated with lower hippocampal grey matter in adults aged 30-56 years (Marsland, et al. 2008). TNF-α exerts a similar antineurogenic effect through interaction with the TNF-R1 receptor (Cacci, et al. 2005; Iosif, et al. 2006; Liu, et al. 2005). Inflammatory blockade restores adult hippocampal neurogenesis (Monje, et al. 2003). Another mechanism by which pro-inflammatory proteins may lead to depression is through induction of the IDO enzyme. IL-6, TNF-α and INF-γ increase the expression of idoleamine 2,3-dioxygenase (IDO) in peripheral and central immune cells. Activated IDO increases kynurenine production from dietary tryptophan and as a consequence reduces the synthesis of serotonin (Heyes, et al. 1992; Mellor and Munn 1999); reduction of serotonin is thought to be a central mechanism in depression. Moreover, increase in metabolic products of kynurenine such as quinolinic acid serves as an NMDA receptor agonist promoting hippocampal neuronal damage and apoptosis (Schwarcz, et al. 1983; Stone and Behan 2007).

Aging is associated with changes in immune responses. In aged mice, lipopolysaccharide injections resulted in prolonged sickness behavior compared to younger adult mice, exaggerated neuroinflammatory response with stronger induction of peripheral and brain IDO and increased turnover in brain serotonin (Godbout, et al. 2005). Discordant central inflammatory responses can have damaging effects to an organism due to the behavioral effects and neurotoxicity of brain pro-inflammatory cytokines (Dilger and Johnson 2008).

Aging of the brain's inflammatory responses may lead to abnormalities in neural systems related to the development of depressive syndromes. In aged rodents, glial cultures from brain sections, including those of areas related to mood processing, have increased inflammatory responses (cytokines IL-6, IL-1β and TNF-α) compared to younger animals after lipopolysaccharide challenge (Terao, et al. 2002; Ye and Johnson 1999). The cerebral cortex of aged mice spontaneously produces higher levels of IL-6 than the cortex of adult animals (Xie, et al. 2003; Ye and Johnson 2001). In older animals, IL-6 is concentrated in the hippocampus, cerebral cortex and cerebellum compared with younger cohorts (Ye and Johnson 1999, 2001).

In normal adults, the inflammatory response to immune challenge may lead to changes in the function of emotional networks. Enhanced activity of the subgenual anterior cingulate cortex and reduced functional connectivity of the subgenual anterior cingulate with the amygdala, medial prefrontal cortex and nucleus accumbens during emotional face processing was shown to be modulated by a peripheral inflammatory response (IL-6) (Harrison, et al. 2009). Moreover, a SNP encoding IL-1β has been associated with both reduced activity of the anterior cingulate and the amygdala in response to emotional probes and with poor response of major depression to antidepressants (Baune, et al.). In addition, patients treated with the cytokine INF-α exhibited greater dorsal anterior cingulate activation than controls (Capuron, et al. 2005); dysfunction of the anterior cingulate has been documented in geriatric depression. These findings suggest a complex interaction between aging, neuroinflammation, and stress such that aging may exacerbate the effects of stress in the CNS leading to behavioral and cognitive changes similar to those characteristic of depressive syndromes.

THE ROLE OF ANTIDEPRESSANTS

There are limited data on the effect of antidepressants on inflammatory processes. Evidence of a relationship between antidepressants and anti-iflammatory processes comes from both preclinical and clinical studies.

Animal studies suggest tricyclic antidepressants (TCA) may reduce the production of some pro-inflammatory and increase the production of anti-inflammatory cytokines. Administration of lipopolysacharide to animals induces “sickness behavior”, a behavioral state with several common symptoms with depression (Yirmiya, et al. 1996). “Sickness behavior” as well as TNF-α production can be attenuated by pretreatment with desipramine (Shen, et al. 1999), although paroxetine and venlafaxine had no significant effects (Shen et al. 1999). In an animal model of anhedonia, pretreatment with TCA reduced pathological behavior. This effect was accompanied by an increase in the anti-inflammatory cytokine IL-10 (Kubera, et al. 1998; Kubera, et al. 2000a; Kubera, et al. 2000b; Kubera, et al. 2001). In the olfactory bulbectomy model of depression, pre-treatment with desipramine decreased the production of the proinflammatory cytokines TNF-α and IL-1β. In animal models of inflammatory diseases septic shock and asthma, the antidepressants fluoxetine and desipramine reduced release of TNF-α (Roumestan, et al. 2007).

In vitro human studies on the effect of antidepressants on cytokine production have yielded contradictory findings. In cell cultures of healthy volunteers, various antidepressants suppressed pro-inflammatory cytokine production. The antidepressants used in these studies were moclobemide (Lin, et al. 2000), clomipramine, sertaline, trazodone (Maes, et al. 1999), imipramine and mianserine (Szuster-Ciesielska, et al. 2003). However, in cell cultures of depressed patients, imipramine, venlafaxine, 5-hydroxy-tryptophan, and a combination of fluoxetine and 5-hydroxy-tryptophan increased IL-6, but not TNF-α production (Szuster-Ciesielska et al. 2003).

Open pharmacological studies and case series suggest that antidepressants influence indices of inflammation, although the direction is unclear. In a small number of depressed patients, fluoxetine and tricyclic antidepressants reduced plasma levels of IL-6 (Basterzi, et al. 2005; Maes et al. 1997). In another small sample, antidepressants decreased IL-12 and increased transforming growth factor beta-1 (TGF β-1) after six weeks of treatment (Lee and Kim 2006). Yet another study showed that antidepressants led to a decrease of the pro-inflammatory cytokines IL-2, IL-6, and TNF-β1 but did not influence INF-γ, IL-4, and TNF-α (Kim, et al. 2007).

Pre-treatment cytokine plasma levels may influence the response to antidepressants. SSRI resistant patients had higher TNF-α plasma levels while euthymic patients with history of depression had TNF-α levels similar to those of normal controls (O’Brien, et al. 2007). Depressed non-responders to escitalopram TNF-α plasma levels had higher TNF-α levels than responders but their levels were similar to normal controls (Eller, et al. 2008). These relationships were most pronounced in males. TNF-α increased in treatment responders during the escitalopram trial and reached the levels of normal subjects. Responders to escitalopram had greater reduction in the soluble IL-2 receptor than depressed non-responders to escitalopram (Eller et al. 2008). However, others failed to detect significant changes in soluble IL-2 receptor levels during antidepressant treatment (Kagaya, et al. 2001; Maes, et al. 1995; Mikova, et al. 2001), although higher soluble IL-2 receptor serum concentrations were found after treatment in non-responders(Mikova et al. 2001).

In summary, some, but not all, antidepressants may reduce “sickness behavior” and production of cytokines in animal models of inflammation. Changes in some cytokines may occur in depressed patients treated with some antidepressants but the relationship of

pretreatment levels to antidepressant response remains unclear. These observations are based mainly on exploratory studies and need confirmation.

THE ROLE OF ANTI-INFLAMMATORY AGENTS

Despite the conceptual appeal of the inflammation theory of depression, few studies have investigated the role of anti-inflammatory agents. However, numerous anti-inflammatory agents have become available recently though limited data exists on their use or effects in psychiatric disorders. What follows summarizes studies of anti-inflammatory agents in neuropsychiatric disorders pertinent to depression.

Minocycline, a semi-synthetic, second-generation tetracycline analog crosses the blood brain barrier and has anti-inflammatory, anti-apoptotic, and antioxidant properties in addition to its bacteriostatic action. The anti-inflammatory effects are both direct and indirect through suppression of microglia activation and proliferation and subsequent release of cytokines IL-1β , IL-6 and TNF-α as well as expression of chemokines such as macrophage inflammatory protein 1α, interferon-inducible protein 10, chemokine receptor 3 as well as suppressing the activity of matric metalloproteases, which disrupt the blood brain barrier (Chen, et al. 2000; Plane, et al.). Minocycline inhibits apoptosis by reducing mitochondrial calcium overload, stabilizing mitochondrial membrane, and inhibiting release of cytochrome c and other apoptotic agents, ultimately resulting in decreased activation of caspase 1 and 3 and lower nuclear damage. An additional antiapoptotic effect of minocycline may be mediated by upregulation of the anti-apoptotic factor BCL-2. The antioxidant effect of minocycline may be mediated in part by inhibition of cyclo-oxygenase 2 induced nitric oxide synthetase and nicotinamide adenine dinuceotide phosphate oxidase. Finally, minocycline inhibits poly-ADP polymerase 1 (PAR 1), a molecule that when activated by DNA damage, contributes to excitotoxicity.

Various experimental models of brain insult suggest that minocycline may have neuroprotective properties. Minocycline may reduce inflammatory indices, brain cell damage and even improve abnormal behavior in models of stroke, Parkinson's disease, Huntington's disease Alzheimer's disease multiple sclerosis, and amyotrophic lateral sclerosis (Plane et al.). However, minocycline was found ineffective or neurotoxic in some animal models especially when very high dosages were used.

Animal studies and anecdotal data suggest that minocycline may possess anti-inflammatory properties. Minocycline has been shown to reduce immobility in mice on the forced swim test, an accepted behavioral model of depression (Molina-Hernandez, et al. 2008). In this same study, a combination of subthreshold doses of minocycline synergized the antidepressant actions of sub-threshold doses of the tricyclic antidepressant desipramine (Molina-Hernandez et al. 2008). Anecdotal evidence suggests that minocycline may augment the action of antidepressants in major depressive disorder (Pae, et al. 2008). An open (Miyaoka, et al. 2008) and a placebo-controlled treatment trial (Levkovitz, et al.) showed that addition of minocycline to an antipsychotic regimen improved symptoms of schizophrenia. Specifically, minocycline reduced overall psychotic and negative symptoms, and improved working memory, cognitive flexibility, and planning in the placebo-controlled study (Levkovitz et al.). While these studies have limitations, they provide the rationale for studying the efficacy of minocycline in geriatric depression, a disorder with brain abnormalities likely to be contributed to at least in part by inflammatory processes.

Etanercept, a soluble TNF-α receptor, prevents TNF-α mediated cellular response by competitively inhibiting the interaction of TNF-α with cell-surface receptors. Etanercept 50 mg twice weekly reduced symptoms of depression in a placebo-controlled study of patients

with psoriasis (Tyring, et al. 2006). While this study had a large number of subjects, only 42 had major depression.

The cyclo-oxygenase-2 inhibitor celecoxib has been found to augment the efficacy of reboxetine, and fluoxetine in patients with major depression (Akhondzadeh, et al. 2009; Muller, et al. 2006). In study of osteoarthritis patients, the cyclo-oxygenase -2 inhibitor rofecoxib reduced symptoms of depression and improved cognition (Collantes-Estevez, et al. 2003). The putative mechanism of celecoxib's action is inhibition of prostaglandin E2 (PGE2). PGE2 stimulated production of IL-6 is increased in depression (Frommberger, et al. 1997; Song, et al. 1998). *In vitro* studies have shown greater PGE2 production by lymphocytes of depressed patients compared to control subjects (Linnoila M. 1983). Moreover, increased PGE2 has been documented in the saliva, serum and cerebrospinal fluid of depressed patients (Akhondzadeh et al. 2009; Nishino, et al. 1989).

THE "INFLAMMATION HYPOTHESIS" IN GERIATRIC DEPRESSION

We propose that aging-related and disease-related processes result in CNS inflammatory changes that may contribute to the etiology of at least some depressive syndromes. Depressed older adults have lower familial prevalence of mood disorders than younger adults and greater cognitive symptoms, structural brain abnormalities, medical morbidity, disability and mortality (Alexopoulos and Kelly 2009). Some of these medical and cognitive events are thought to predispose patients to geriatric depression and may be fueled by a CNS pro-inflammatory state. Accordingly, we suggest that immune processes are likely to promote changes in the emotional and cognitive neural systems predisposing to geriatric depression or facilitate the metabolic brain changes mediating the depressive syndrome in late life. We base this assertion on converging findings suggesting that:

1. Aging results in increased peripheral immune responses, impaired peripheral-CNS immune communication, and a shift of the CNS into a pro-inflammatory state with exaggerated and prolonged responses to immune challenge.
2. Exaggerated and prolonged immune responses of the CNS can influence the function of some of the emotional and cognitive networks pertinent to geriatric depression.
3. Aging of the brain's inflammatory responses leads to behavioral changes reminiscent of the depressive and cognitive symptoms of geriatric depression.
4. Some antidepressants reduce the expression of several inflammation markers in the periphery.
5. Limited data suggest that some anti-inflammatory agents may have antidepressant properties.

TESTING THE INFLAMMATION HYPOTHESIS IN GERIATRIC DEPRESSION

Available findings provide a "signal" of a relationship between aging of the brain's immune system, medical comorbidity increasing the brain's pro-inflammatory state and geriatric depression. However many questions remain to be answered, including:

1) Is the aging- and disease-related CNS pro-inflammatory state, indeed, an etiological factor of some geriatric depressive syndromes or a consequence of the pathophysiological changes of depression? If CNS inflammation is etiologically related to geriatric depression, what position does it occupy in the chain of biological events leading to the syndrome?

2) Do aging and disease-related CNS pro-inflammatory states influence the short-term or long term course of geriatric depression?

2) Is the pro-inflammatory state in aging related to a specific depressive symptom set or to abnormalities of specific cognitive or emotional networks that function abnormally in depression?

3) Do older persons with structural or functional brain abnormalities predisposing to poor antidepressant response have increased indices of inflammation?

4) Do high pretreatment levels of inflammation indices influence response to antidepressants?

5) Is improvement of geriatric depression accompanied by reduction of inflammatory markers?

6) Which anti-inflammatory agents, if any, have antidepressant action and which such agents can augment the action of conventional antidepressants in resistant depression?

The “inflammation hypothesis” of geriatric depression as proposed above cannot be tested. It can, however, lead to testable hypotheses on mechanisms by which the aging of CNS immune system promotes geriatric depression. Developments, including information on the neurobiology of depression, availability of PET ligands of neuroinflammation, advanced animal models, and the emerging pharmacology of anti-inflammatory agents provide the means to answer some of these questions and may hopefully lead to a novel treatment model.

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