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Brief Commentary

The impact of aging on the brain – risk, resilience and repair

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None declared.

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The world is getting older; just less than 1 in every 8 citizens in the US is 65 years or older and it is estimated that, by 2030, 1 in every 5 citizens will be 65 years or older. These figures are replicated in most western countries. This inexorable increase in the aging population is accompanied by increased risk of age-related diseases including neurodegenerative diseases, but also cardiovascular disease and diabetes which increase the likelihood of developing conditions that impact on neuronal function. Aging also affects resilience and the consequences of any insult, including trauma, stress, infection or surgery can have profound effects in an aged individual. The underlying cause of this age-related decrease in resilience may be a consequence of immunosenescence, which is associated with constitutive, though low-grade, inflammation (inflamm-aging) compromising the health of the elderly (McElhaney and Effros, 2009).

It is well documented that the effects of infection are more profound in aged, compared with young, animals (Barrientos et al., 2006; Frank et al., 2009) and that resolution of infection is protracted in aged individuals. Studies in aged animals have demonstrated that this results from diminished ability of the cells of the immune system to respond to insult. In older humans, influenza is associated with increased mortality, delayed recovery and sometimes sequelae which diminish quality of life. Studies in aged mice suggest that the slower recovery following influenza infection is associated with a delay in recruitment of granulocytes into the lung accompanied by more persistent macrophage infiltration (Toapanta and Ross, 2009). However immunosenescence is associated with changes in numbers and function of several immune cell subsets. Overall numbers of B cells and T cells decrease with age, although an increase in memory T cells, in particular CD8⁺ T cells, occurs. The relatively poorer antibody response to influenza vaccination in aged individuals has been linked with an increase in the proportion of CD8⁺ CD28⁻ cells (Saurwein-Teissl et al., 2002). An increase in these cells also occurs in aged
individuals with latent cytomegalovirus (CMV) infection (Almanzar et al., 2005). In turn, the age-related changes in the immune system can reactivate CMV and related viruses triggering further inflammatory changes (Bennett et al., 2012). Age-related changes in natural killer (NK) cell function have also been described; the numbers of NK cells and NKT cells increase and the evidence indicates that NKT cells prepared from livers of aged mice secrete more IL-17 than cells prepared from young mice. The increase in mortality in aged mice infected with systemic herpes viruses has been attributed to these changes (Stout-Delgado et al., 2009).

Systemic infection also alters the course of neurodegenerative diseases and evidence suggests that infection may precipitate relapse or even trigger the onset of multiple sclerosis (Stratton and Wheldon, 2006). Infection has been reported to accelerate cognitive decline in patients with Alzheimer’s disease (Holmes et al., 2003) and it has been suggested that infiltration of C. pneumoniae into the brain may precipitate the disease (Stallings, 2008). Penetration of the microorganism into the brain is not required, however, for induction of CNS complications. Communication pathways between the peripheral immune system and brain (e.g., vagal afferents) are also critical during infection, as they stimulate brain microglia to produce inflammatory mediators that drive disease pathogenesis and behavioral pathology (Dantzer et al., 2008).

It seems likely that immunosenescence occurs in the CNS as well as in the periphery and the key change is microglial dysfunction; the result of this is an impaired ability of these cells to provide neuroprotection and, ultimately, the development of neurodegenerative changes (Streit and Kincaid-Colton, 1995). There is little doubt that the well-described age-related neuroinflammatory changes are accompanied by microglial activation. Thus microglia in the
brain of aged individuals express cell surface markers that are indicative of activation; these markers include CD11b which plays a role in cell mobility and chemotaxis, CD68 which may reflect phagocytic function and MHCII which indicates antigen presentation function. It appears that age-related changes in expression of these and other markers of activation are region-specific, with more pronounced changes in caudal areas of the brain and in white matter (Hart et al., 2012). The phenotypic changes in microglia render them hypersensitive to infectious agents and to signals derived from the peripheral immune system. This is a significant event leading to behavioral pathology in aged rodents with an infection. This is also likely to be the case in humans because acute cognitive disorders are common in older adults with peripheral infections (Chiovenda et al., 2002; Wofford et al., 1996). It has been consistently reported that aged animals, or microglia from aged animals, respond more profoundly to activation of Toll-like receptor (TLR)4 by lipopolysaccharide (LPS) and TLR2 by PamCSK3 exhibiting an increase in inflammatory cytokine production (Chen et al., 2008; Njie et al., 2012). Treatment of aged animals with LPS also exerts a greater effect on hippocampal-dependent behavioral tasks (Chen et al., 2008), sickness behavior (Godbout et al., 2005), as well as depressive-like behavior (Godbout et al., 2008).

It is now recognized that, like macrophages, microglia can adopt a number of activation states (Colton, 2009); whereas inflammatory changes occur when the innate immune response is triggered, for example by activation of TLRs and when interferon-γ (IFNγ) stimulates classical activation, changes which play a role in resolution of inflammation occur when the alternative activation state is stimulated by anti-inflammatory cytokines like IL-4 (Colton, 2009). Thus we must now consider the possibility that age-related microglial activation may be multifaceted with
altered response profiles, not only to LPS, but also to other stimuli, for example IL-4 (Fenn et al., 2012).

Under resting conditions, microglia are maintained in a deactivated state which relies on the presence of IL-10 and transforming growth factor-β (TGFβ) in the microenvironment and, in addition, the interaction of microglia with other cells enabled by interaction between ligand-receptor pairs further ensures that microglia remain quiescent. In this context, a role for CD200-CD200R interaction has been reported and the evidence indicates that the age-related decrease in CD200 expression is associated with activation of microglia and inflammatory changes (Lyons et al., 2007) and loss of synaptic contacts (Ojo et al., 2012), which impact on cognitive function.

There is now general acceptance that the immune system and the CNS are inextricably linked (Romo-Gonzalez et al., 2012) and this link is consolidated by the observation that interventions which benefit one system also benefits the other. For example, the anti-inflammatory effects of exercise, and consequent improvements in health are well described (Gleeson et al., 2011) as are its beneficial effects on cognitive function. Accordingly, voluntary exercise in aged mice has been reported to shift the microglial phenotype towards neuroprotection (Kohman et al., 2012) and, in older adults, cardiovascular fitness is associated with reduced brain atrophy and improved cognitive function (Weinstein et al., 2012). Likewise, polyunsaturated fatty acids like docosahexaenoic acid, which have powerful anti-inflammatory actions, are known to improve cognitive function in aged individuals (Karr et al., 2011).

This issue of Brain, Behavior and Immunity includes an assemblage of 12 original research articles related to aging and psychoneuroimmunology. They run the gamut from transcriptional profiling in glial cells from aged mice (Kremsky et al., 2012) to in vivo
assessment of brain atrophy by magnetic resonance imaging, to understanding how cardiovascular fitness improves cognition in elderly humans (Weinstein et al., 2012). Suzanne Segerstrom studied a cohort of older adults who received annual influenza vaccinations and found that distress and vulnerability interact affecting a number of post-vaccine responses (Segerstrom et al., 2012), while Bennett and colleagues present evidence suggesting that reactivation of multiple herpesviruses in older adults leads to increased inflammation (Bennett et al., 2012). These findings carry added significance now that we know peripheral infection and inflammation impinge upon the brain causing microglia with an activated phenotype to overreact. A collection of studies presented herein focused on the mechanisms responsible for age-related changes to microglia. They advance our understanding of age-related microglial dysfunction by showing impaired neuron-microglial cross-talk (Cox et al., 2012; Ojo et al., 2012), revealing activated microglia from aged mice are less sensitive to the anti-inflammatory and M2-promoting effects of IL-4 (Fenn et al., 2012), and showing, for the first time, that microglial phenotype and function vary significantly between CNS compartments in aged mice (Hart et al., 2012). Results of another study suggest that excessive production of IL-6 in the brain of aged mice is paralleled by increased IL-6 receptor trans-signaling, which leads to cognitive deficits (Burton and Johnson, 2012). The good news is that there appear to be several pragmatic lifestyle changes that reduce neuroinflammation and improve cognitive aging—exercise and improved cardiovascular fitness (Kohman et al., 2012; Weinstein et al., 2012) and consuming a diet rich in anti-inflammatory n-3 polyunsaturated fatty acids (Luciano et al., 2012; Moranis et al., 2012).
References


This Brief Commentary describes a Special Issue that features a series of papers that provide new data on how aging and inflammation interact to affect behaviors that are regulated by the dialogue between the immune system and the brain.