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Peripheral Inflammation and Cognitive Aging

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Abstract

Evidence suggests that inflammation, an innate immune response facilitating recovery from injury and pathogenic invasion, is positively associated with age-related cognitive decline and may play a role in risk for dementia. Physiological pathways linking the peripheral immune and central nervous systems are outlined, and studies linking inflammation with neurocognitive function are overviewed. We also present recent studies from our laboratory showing that midlife inflammation is related to cognitive function and brain morphology. Finally, potential implications for treatment, future directions, and limitations are discussed.

Age-related cognitive decline is characterized by the gradual and progressive deterioration of several domains of cognitive ability, including executive function, working and episodic memory, processing speed and attention [1]. Compared to younger individuals, elderly adults perform significantly worse on tasks involving delayed recall [2], recognition [3] and mental flexibility [3, 4]. These declines typically begin in middle adulthood and progress at a consistent rate across the rest of life [5]. In addition to negatively impacting the quality of life of older adults, deteriorating cognitive function imposes significant risk for dementia, injuries, hospitalization and death [5, 6]. Accordingly, recent research has focused on the identification of factors that predict risk for age-related cognitive decline and may be targeted by preventative intervention. In this regard, it is known that traditional cardiovascular risk factors contribute to the prediction of risk for accelerated neurocognitive aging. Recent evidence suggests that systemic inflammation may also play a role [7–9]. In this chapter, evidence linking inflammation with neurocognitive function will be overviewed, with a particular focus on recent work highlighting morphometric brain changes that accompany the elevations in peripheral inflammatory activity that occur in later life.

Acute Inflammatory Response and Chronic Systemic Inflammation

The acute inflammatory response is initiated when tissue-residing macrophages are activated by tissue damage or pathogen invasion, resulting in the release of several pro-inflammatory cytokines including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α). Locally,

these cytokines serve several functions, including stimulating the expression of epithelial adhesion molecules, increasing vascular permeability, and supporting leukocyte trafficking through chemotactic signaling. Proinflammatory cytokines also enter the peripheral circulatory system and are involved in signaling a systemic inflammatory response characterized by hepatic synthesis and release of acute-phase proteins including C-reactive protein (CRP) [10, 11]. Although TNF-α and IL-1β decay rapidly, IL-6 and CRP have longer half-lives and are reliably detected in human plasma/serum. In the absence of acute infection, it is widely accepted that circulating concentrations of IL-6 and CRP reflect an index of chronic system-wide inflammation at the time of the blood draw. Although generally stable over extended periods, circulating levels of IL-6 and CRP increase with age and predict risk for accelerated cognitive decline among elderly populations [12].

Pathways Linking the Peripheral Immune and Central Nervous Systems

For several decades, it was believed that the immune system and the brain functioned in isolation due to the anatomical separation of leukocytes from the central nervous system (CNS) by the blood-brain barrier. More recent evidence, however, challenges this notion and shows that peripheral inflammatory mediators exert an influence on brain function and play a critical role in the induction of sickness symptoms that accompany inflammatory disease. For example, human research shows that systemic infusion of IL-1 and TNF-α leads to suppression of food intake, decreased social exploration, and poorer memory consolidation [13–15]. Impairments in cognitive function have also been observed in murine models following the peripheral administration of lipopolysaccharide (LPS) – an endotoxin that stimulates the release of proinflammatory cytokines [16]. Together, results from these and other studies have led to current understanding that peripheral cytokines elicit an array of affective, behavioral, and cognitive adaptations that facilitate recovery during the course of acute infection. Three distinct molecular pathways link peripheral immune stimuli to changes in the CNS. First, peripheral cytokines can activate vagal afferent nerves that stimulate the production of proinflammatory cytokines by central tissues [17]. Second, peripheral cytokines can stimulate brain vascular endothelial cells to release secondary messengers in the CNS that promote the central release of proinflammatory cytokines [18]. Finally, peripheral cytokines can be actively transported in the paraventricular regions of the blood-brain barrier [19]. These pathways provide a link between the peripheral expression of proinflammatory cytokines in response to infection or injury and the central immune responses that result in sickness behaviors that include neurocognitive symptoms.

Inflammation in the Central Nervous System: Animal Studies

Along with the transient affective and behavioral symptoms that accompany acute illness, neuroinflammatory processes in the brain play a role in the long-term modulation of neurocognitive function and age-related cognitive decline [20]. Despite distinct morphological differences, microglial cells and macrophages are derived from common progenitor cells and serve analogous roles in their respective systems [21]. When activated by proinflammatory cytokines microglial cells adopt an inflammatory phenotype that resembles activated macrophages, including the expression of surface antigens and the production of central proinflammatory cytokines [22–24]. Of particular relevance for neurocognitive processes, receptors for proinflammatory cytokines are highly expressed on microglia found in the hippocampus and prefrontal brain regions [25–27].

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Elevations in central proinflammatory cytokines interfere with a variety of neuromolecular processes, including hippocampal neurogenesis, long-term potentiation (LTP), synaptic plasticity, and synaptic scaling [28], and eventually result in dendritic atrophy with negative consequences for learning and memory [29, 30]. For example, central administration of IL-1 impairs performance on some [31–33], but not all [34, 35] hippocampal-dependent spatial learning tasks. Similarly, transgenic mice that overexpress central levels of IL-6 show deficits in synaptic plasticity and impaired avoidance learning [36], whereas the administration of IL-6 receptor antagonists to intact mice prevents the decreases in hippocampal LTP and neurogenesis, and the subsequent cognitive sequelae that accompany peripheral and central inflammation [37]. Taken together, these findings suggest that proinflammatory cytokines play a critical role in modulating the neuromolecular processes that underlie cognitive processes, such as learning and memory.

Much of the early animal literature focused on the impact of acute inflammatory processes on cognitive function; however, recent attention has turned to the consequences of chronic elevations in inflammation that more closely resemble the changes that accompany aging. Here, studies show that chronic stress results in an increase in peripheral inflammation that sensitizes or 'primes' a proinflammatory shift in microglial phenotype, resulting in an increase in central proinflammatory cytokines and concomitant deficits in learning and memory [38, 39]. For example, mice subjected to social isolation over a 4-week period show elevated levels of hippocampal IL-1β, decreased hippocampal neurogenesis, and specific impairment of hippocampal-dependent memory [40]. It is also suggested that age-related elevations in systemic inflammation affect cognitive function [41]. Aging has been associated with proinflammatory cytokine expression in the periphery [42], IL-6 levels in hippocampal and prefrontal brain regions [43], and activation of microglia [44]. Furthermore, when compared with younger mice, aged mice show greater elevations in central cytokine expression and larger deficits in cognitive performance following peripheral immune challenge [45]. In sum, animal evidence suggests that age-related microglial activation results in exaggerated central responses to peripheral inflammation, which may play a role in the neurocognitive decline that accompanies aging [46].

Inflammation in the Central Nervous System: Human Studies

In humans, several independent lines of experimental and epidemiologic research support a role of inflammation in the modulation of cognitive function. Utilizing a similar approach to the animal research, a number of experimental studies have examined the cognitive sequelae of acute immune activation. This technique typically involves examining changes in cognitive performance that accompany the peripheral administration of an inflammatory stimulus. For example, in an early study, Reichenberg et al. [29] administered low-dose *Salmonella abortus equi* endotoxin and saline placebo to 20 male volunteers in a double-blind balanced crossover design. When compared with response to saline, endotoxin was associated with significant impairments in cognitive performance. Furthermore, this effect was dependent on the magnitude of the IL-6 response, with higher responses predicting the greatest impairments in performance. Similar patterns of results were reported in subsequent studies by Krabbe et al. [42] and Brydon et al. [47] that examined the impact of low-dose *Escherichia coli* endotoxin and typhoid vaccination, respectively. Both studies found inverse associations of IL-6 production and performance on declarative memory and executive function tasks. Finally, more direct evidence for a role of IL-6 comes from a study conducted by Spath-Schwalbe et al. [48], which showed that peripheral administration of recombinant IL-6

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decreased self-reported attentional capacity when compared to placebo. Findings from these human experimental studies parallel results from animal models, and show that acute elevations in peripheral inflammation are accompanied by declines in several cognitive domains including memory, attention, and executive function.

Corroborating experimental evidence, epidemiological studies also support an inverse association of peripheral inflammation with cognitive function. Insight can be derived from studies of neurodegenerative diseases that typically involve deficits in memory, including Alzheimer's disease and vascular dementia. These syndromes are generally associated with higher than normal circulating levels of CRP, IL-6, and IL-1β [49–51]. For example, Zuliani et al. [52] showed that compared to healthy individuals, those diagnosed with dementia had higher levels of circulating TNF-α, IL-1β, and IL-6. Cross-sectional studies of this nature do not shed light on the direction of the observed associations. Indeed, it is plausible that elevations in peripheral cytokines may reflect a consequence, rather than a cause, of neurodegenerative processes [42, 53].

To disentangle these possibilities, prospective longitudinal designs have been utilized. In general, these studies show that peripheral inflammation predicts future cognitive declines and subsequent risk for Alzheimer's disease and other dementias [54, 55]. For example, a recent study showed that compared to healthy participants, individuals with midlife rheumatoid arthritis, a chronic inflammatory condition associated with elevated levels of IL-6, have a 1.96-fold greater risk for developing mild cognitive impairment, and a 2.43-fold increased risk for developing Alzheimer's disease over a 20-year follow-up period [56]. Likewise, midlife levels of circulating CRP and production of IL-1β and TNF-α by stimulated peripheral blood cells have been positively linked with risk for Alzheimer's disease and vascular dementia in late life [57, 58]. Although most studies suggest that inflammation predicts future risk for dementia, not all findings are consistent. For example, plasma CRP levels were unrelated to dementia risk among older adults followed over a 13-year period in the Framingham Heart Study [59].

In addition to clinical studies of dementia, a growing literature suggests an association of proinflammatory cytokines with normative variation in cognitive function. While the specific assessments of cognitive ability vary, several studies show inverse associations of proinflammatory markers and cognitive functioning [60–63], but again, not all results are consistent [64, 65]. Reasons for these inconsistencies are unclear, but it is speculated that age may play a moderating role [66–68], with the progressive increases in peripheral inflammation that occur across adult life accelerating neurocognitive aging. However, to date, most studies have examined these associations in the elderly when issues relating to differential survivorship, immunoscenescence, and existing health conditions complicate the picture. Findings from longitudinal studies that examine inflammation in midlife are more consistent, and show that accelerated patterns of cognitive decline and increased risk for dementia accompany higher levels of systemic inflammation [57, 69].

Interleukin-6 and Cognitive Performance among Midlife Community Volunteers

We have reported some of the first findings to show an inverse association of plasma IL-6 with working memory/attention and executive function among healthy middle-aged adults [70]. In this study, we recruited 500 community volunteers (age 30–54; 51% male) and drew blood samples for the assessment of plasma IL-6 levels. Subjects also completed a battery of neuropsychological tests to assess memory and executive function. Based on animal findings showing that peripheral proinflammatory cytokines interfere with hippocampal processes and evidence that

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