NEURO-INFLAMMATION AND ITS EFFECTS ON COGNITION: A REVIEW OF LITERATURE

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ABSTRACT

Introduction: More and more evidence suggests that inflammation is positively associated with age-related cognitive decline and may play a role in the development of dementia. Method: Physiological pathways linking the immune system to the central nervous system are reviewed in this article and studies regarding the association between inflammation and neurocognitive function are reviewed from literature. Results: Recent studies show that midlife inflammation is related to cognitive function and brain morphology. Human studies combining different markers of inflammation, neuroimaging methods and cognitive tests are consistent with studies on animal models which conclude that inflammation contributes to lowering cognitive performance over and above more traditional cardiovascular risk factors such as: hypertension, metabolic factors, smoking and subclinical atherosclerosis. The studies reviewed had limitations by not estimating the impact of multiple factors known to affect circulating levels of inflammatory mediators such as: acute inflammatory disease, psychological stress or physical activity. Conclusions: Circulating markers of inflammation predict future risk of cognitive decline and possibly contribute to the pathophysiology of preclinical neurocognitive decline. Key words: inflammation, cognitive decline, dementia, neuroimaging.

INTRODUCTION

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). These declines typically begin in middle adulthood and progress at a consistent rate across the rest of life and they include worse scores on tasks involving mental flexibility, recognition and delayed recall (1, 2, 3). What is more, deterioration in cognitive function has a negative impact on quality of life and imposes significant risk for dementia, injuries, hospitalization and death (1,2,3).

Recent research (4,5,6) has focused on identifying modifiable risk factors of age-related cognitive decline and evidence suggests that systemic inflammation may also play a role in this process, in opposition with the old paradigm 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 (BBB). As such, impairments in cognitive function were observed in animal models following peripheral administration of endotoxin (7), findings that were also confirmed in human studies where systemic infusion of IL-1 and/or interferon alpha lead to decreased social exploration and suppression of food intake (8-10).

At least three distinctive molecular pathways were...
identified linking peripheral immune stimuli to changes in the CNS. In the first case, peripheral cytokines stimulate brain vascular endothelial cells to release secondary messengers in the CNS that, in term, promote central release of proinflammatory cytokines (11). Another pathway is represented by peripheral cytokines that activate vagal afferent nerves to stimulate the production of proinflammatory cytokines via signals form the nucleus tractus solitarius (12). The third pathway is represented by peripheral cytokines which can be actively transported in the paraventricular regions of the BBB (13) and from there into the CNS. These pathways provide a link between the peripheral expression of proinflammatory cytokines and the central immune responses which can cause neurocognitive symptoms.

**CYTOKINE INVOLVEMENT**

The acute inflammatory response is initiated when macrophages are activated by pathogen invasion or tissue damage, resulting in the release of several proinflammatory cytokines such as interleukin-10 (IL-10), IL-6, and tumor necrosis factor-a (TNF-a). Pro-inflammatory cytokines also enter the peripheral circulatory system and cause a systemic inflammatory response characterized by hepatic synthesis and release of acute-phase proteins including C-reactive protein (CRP) (14, 15). Although TNF-a decays rapidly, IL-6 and CRP have longer half-lives and are reliably detected in human plasma serum. What is more, it has been shown that circulating levels of IL-6 and CRP increase with age and predict the risk of accelerated cognitive decline among the elderly (16). For example, transgenic mice that overexpress central levels of IL-6 show deficits in synaptic plasticity and impaired avoidance learning (17) and the administration of IL-6 receptor antagonists to normal mice prevents the decrease in hippocampal long-term potentiation (LTP), neurogenesis and the subsequent cognitive sequelae that accompany peripheral and central inflammation (18). Taken together, these findings suggest that proinflammatory cytokines play a critical role in modulating the neuro-molecular processes involved in cognitive functioning such as learning and memory.

**CHRONIC STRESS AND MICROGOLIA**

Another factor that can alter cognitive function is chronic stress (including low socioeconomic status, loneliness and caregiving for a terminally ill family member) (19) because it has been shown to increase 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 (20, 21). Studies on mice exposed to social isolation over a 4-week period presented elevated levels of hippocampal IL-1F, decreased hippocampal neurogenesis and specific impairment of hippocampal-dependent memory (22).

**AGE**

The aging process is considered to be associated with a proinflammatory status giving raise to cytokine expression in the periphery (23). IL-6 in hippocampal and prefrontal brain regions (24) and activating the microglia (25). Also, receptors for proinflammatory cytokines are highly expressed on microglia found in the hippocampus and prefrontal brain regions (26-31). Animal studies suggest that age-related microglial activation results in exaggerated central responses to peripheral inflammation, which may play a role in the neurocognitive decline that accompanies the aging process (32).

**INFLAMMATION VIA ENDOTOXIN ADMINISTRATION**

The most used methodology in human studies involves examining changes in cognitive performance that accompanies the peripheral administration of an inflammatory stimulus. For example, a double-blind, balanced, crossover study split 20 male subjects in an intervention group (that received Salmonella endotoxin) and placebo (that received saline) (33) showing significant impairments in cognitive performance in the intervention group. Moreover, the effect was dependent on the level of the IL-6, with higher responses predicting the greatest impairments in performance. Similar results were reported in subsequent studies by Krabbe et al. (using Escherichia coli endotoxin vaccination) (23) and later confirmed by Brydon et al. (with typhoid vaccination) (34) with both studies finding 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. which showed that peripheral administration of recombinant IL-6 decreased self-reported attentional capacity when compared to placebo (35). While the specific assessments of cognitive ability may vary, several other studies show inverse associations of proinflammatory markers and cognitive functioning (36-39).

**INFLAMMATION STATUS OF PATIENTS WITH DEMENTIA**

Some insight regarding this topic comes 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-1F (22, 40). For example, Zuliani et al. (40) showed patients diagnosed with dementia had higher levels of circulating TNF-a, IL-1B and IL-6 compared to healthy individuals. It is plausible that elevations in peripheral cytokines may reflect a consequence rather than a cause of neurodegenerative processes (41). Studies with longitudinal design showed that peripheral inflammation predicts future cognitive declines and subsequent risk for Alzheimer’s disease and other dementias (42). For example, a recent study showed that people with a chronic inflammatory condition like rheumatoid arthritis, have elevated levels of IL-6 (when compared to healthy participants) and have a 1.96-fold greater risk for developing mild cognitive impairment and a 2.43-fold increased risk for developing Alzheimer disease over a 20-year follow-up period (43). These results are confirmed by others studies that show that midlife levels of circulating CRP and peripheric production of TNF-a have been positively linked with increased risk for Alzheimer’s disease and vascular dementia in late life (44, 45). On the other hand, in the Framingham Heart Study plasma CRP levels were unrelated to dementia risk among older adults followed over a 13-year period (45).

These findings contribute to a growing data that links chronic inflammation to poor cognitive functioning. It also raises the possibility that high levels of circulating cytokines could be a biomarker of future risk for accelerated cognitive decline.

**WHITE MATTER LEISONS AND MRI FINDINGS**
Other studies have extended the assessment of inflammation-related brain structures to an examination of white matter hyperintensities (WMH), providing a marker of white matter damage and lesions (46). The older the subjects the higher the WMH value (47) and it has also been proven that this mark predicts future incidence of stroke, dementia, cognitive decline and death (48). The possibility that inflammatory processes may play a role in age related increases of WMH has been the focus of several recent investigations (49, 50). Additionally, IL-6 and, to a lesser extent, CRP were positively associated with WMH volume.

A recent study by Furney et al. (51) examined the contribution of structural MRI results of inflammation in predicting the risk for dementia. Although cytokine levels and MRI findings contributed independently to the prediction of risk, a model that combined them both accounted for greater predictability. There are many congruent proofs that inflammation plays a role in progression to dementia and these findings raise the question if the traditional structural MRI techniques may not adequately detect the entirety of inflammatory-related effects.

OBESITY
In addition to immune cells, adipose tissue is a key contributing source of proinflammatory mediators, including IL-6, explaining why high BMI is also associated with age-related cognitive decline (52) and risk for future dementia (53). Thus, it is plausible that interventions aimed at reducing adiposity may protect against cognitive impairment. While weight loss by dieting and bariatric surgery has been associated with reductions in peripheral inflammation (54), it is unknown whether the magnitude of these effects conveys protection against accelerated cognitive aging.

Findings also suggest that anti-inflammatory drugs can restore hippocampal neurogenesis in rats and other human epidemiological evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may slow the progression of memory loss in patients with dementia and decrease the future risk for Alzheimer's disease. Until now, most of these clinical trials have focused on secondary prevention in elderly populations who are already diagnosed with dementia, but results from a recent study showed that anti-inflammatory drugs could protect against age-related atrophy of grey and white matter among older women (55). However, not all findings are consistent as there are clinical trials that show no benefit of NSAIDs in preventing cognitive decline in patients with dementia (56). It remains to be determined whether NSAIDs are beneficial if provided earlier in the disease course.

LIMITATIONS
While some prospective longitudinal designs have been utilized, studies investigating associations of inflammation and cognitive function are largely cross-sectional, precluding causal interpretations. Animal studies support the role of inflammation in modulating cognitive performance, however the reverse is also a possibility with elevations in peripheral inflammation from neurodegenerative processes in the CNS, but this can also be a 'spillover' effect (57). It is also possible that associations may stem from a third factor, possibly relating to individual differences in genetics.

Another limitation of the current literature is the use of single set assessments of inflammatory markers. Evidence suggests that these markers are relatively stable over extended periods (58), however, multiple factors are known to impact circulating levels of inflammatory mediators, including acute inflammatory disease, psychological stress, and physical activity. Thus, a more reliable assessment of stable individual difference would be derived from assessing means across multiple testing occasions.

CONCLUSIONS
The studies overviewed in this article suggest that circulating markers of inflammation can predict the risk of cognitive decline and can possibly contribute to the pathophysiology of preclinical neurocognitive decline. Recent human studies combining different markers of inflammation, neuroimaging methods and cognitive tests are consistent with studies on animal models showing that inflammation contributes to lowering cognitive performance. However, because inflammation varies significantly in elderly and they also have more cardiovascular risk factors, predictive factors of cognitive decline are very difficult to pin-point.

Future prospective investigations are needed, which begin in middle adulthood and examine inflammation, brain structure and cognitive function, in order to assess if variation in systemic inflammation among adults represents a risk for accelerated cognitive decline and dementia, shedding light on possible neural pathways of these processes.

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