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GUEST COMMENTARY

Neuroinflammation and Cognitive Dysfunction in Chronic Disease and Aging

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Inflammation is a normal reaction to injury that serves to protect an organism and promote repair. Inflammation is also a prominent feature of many age-associated diseases including arthritis, cardiovascular disease, diabetes and even cancer. In these conditions inflammatory mediators and cells that respond to ongoing injury can themselves promote further injury and dysfunction. The same is true in the brain where neuroinflammation, a process characterized by activation of glial cells and release of inflammatory mediators such as cytokines, chemokines, and prostaglandins, can be

harmful and even toxic. For example, many researchers have considered neuroinflammation to be at least a contributing factor to the progression of Alzheimer's disease (AD) for two decades now. In AD, activated glial are found clustered around amyloid plaques, and elevated levels of cytokines and other inflammatory mediators found in patients with AD have been proposed to contribute to ongoing pathology, neural dysfunction, and synaptic loss (Mrak and Griffin, 2005; Agostinho et al., 2010; Heneka et al., 2010). More recently, neuroinflammation has also been recognized as a potential part of normal aging (Lucin and Wyss-Coray, 2009; Jurgens and Johnson, 2010). Much research has therefore been aimed at understanding whether inflammatory processes are a causative or contributing factor to pathophysiology and memory loss in AD and cognitive decline that can occur in normal aging.

The idea for this special edition arose from a symposium held in late 2010 at the University of Rochester School of Medicine & Dentistry. Supported by the Schmitt Foundation for Integrative Brain Research, this symposium brought scientists together to share data and discuss new research directions. The aim of the symposium was to assess the role of neuroinflammation in the molecular pathology and behavioral memory impairments resulting from aging and a variety of chronic diseases, with the hope of elucidating new avenues for research. A number of the authors in this issue were present at the symposium, including Drs. Lynch, Bilbo, O'Banion, and Bowers. Also presenting at the symposium was Dr. Howard Gendelman, Editor-in-Chief of the *Journal of Neuroimmune Pharmacology*, who promoted the idea of expanding the presentations and discussions held at the symposium so that they could be shared with a wider audience. The resulting compilation of articles herein, including reviews, brief reports, and primary research articles, draws attention to the importance of proper inflammatory regulation in the CNS for normal cognitive function and suggests that disruption of homeostasis may contribute to certain CNS disorders. Only by understanding the complex regulation of neuroinflammation across the lifespan will researchers have success in targeting this system for critical therapeutic benefit.

A number of reports now demonstrate that neuroinflammation, in fact, can be associated with normal aging (Ye and Johnson, 2001; Frank et al., 2006; Sierra et al., 2007). Furthermore, age itself can act to prime the CNS, leading to an exaggerated inflammatory response and deleterious outcome following a low-grade inflammatory challenge (Barrientos et al., 2006; Chen et al., 2008; Godbout and Johnson, 2009). Two reviews in this special edition address the influence of age on immune regulation within the CNS. Corona et al. (2011) review the current literature in this area, with particular emphasis on a number of immune regulators that are influenced by age. They focus on behavioral and cognitive alterations from the exaggerated inflammatory response with aging. Continuing the discussion of age and the immune system, Bilbo et al. (2011) examine immune regulation at the other end of the aging spectrum—during development. They review literature detailing how inflammation early in life can impact the developing immune system with lasting neurocognitive effects into adulthood. These reviews highlight the interplay between age and the immune system and demonstrate the negative effects they can have on cognitive function and neurologic disease.

Amyloid precursor protein (APP) is commonly known for its role as the source of beta amyloid in the brain, and is therefore a critical player in the formation of amyloid plaques in AD. However, many tissues and cell types outside of the brain express APP. Puig et al. (2011) examine the influence of APP on inflammatory cells and intestinal function *in vitro* and *in vivo*. Intestines from APP knockout mice have reduced expression of inflammatory markers, basal cytokine secretion, and evidence of macrophage infiltration. *In vivo*, intestines from APP knockout mice show a functional impairment in absorption and increased motility. These studies help elucidate the normal physiological functions of APP and may provide novel insight for its role in AD.

To understand how inflammation specifically impacts the CNS, the key immune molecules involved must be investigated. A number of immune-related molecules have been highlighted in this issue, including interleukin-1 (IL-1), nitric oxide, tumor necrosis factor (TNF) alpha, and prostaglandins. IL-1 is a proinflammatory cytokine that can initiate a cascade of inflammatory events. Dr. O'Banion's laboratory presents two papers in this issue describing behavioral, molecular, and structural effects following prolonged overexpression of this powerful cytokine in a transgenic mouse model. Following 3–6 months of IL-1 beta overexpression within the hippocampus, Hein et al. (2011) show significant memory impairments and hyperactivity, with reduced hippocampal volume at 6 months. When these transgenic mice were crossed to mice overexpressing APP/PS1, 1 and 3 months of hippocampal IL-1 beta overexpression reduced amyloid beta plaques in the brain, indicating a potentially protective role of IL-1 and inflammation in models of Alzheimer's disease (Matousek et al., 2011).

Of course, other immune mediators, including nitric oxide and TNF alpha, are also important in inflammation-induced cognitive dysfunction and chronic disease. Examining one of these mediators, nitric oxide, in an AD model, Kummer et al. (2012) report primary *in vitro* and *in vivo* data demonstrating that nitric oxide synthesizing enzyme activity negatively regulates amyloid beta degrading enzymes. Montgomery and Bowers (2011) expound the current understanding of TNF alpha function within the CNS under normal physiologic conditions and how it changes with neurodegenerative disorders, particularly multiple sclerosis, AD and Parkinson's disease. Importantly, they review recent preclinical and clinical

findings of drugs that have targeted TNF alpha in these diseases.

While chronic use of non-steroidal anti-inflammatory drugs, which inhibit the production of prostaglandins, reduces the risk of developing AD, treatment of patients already demonstrating cognitive impairment has failed to slow or reverse disease progression (Heneka et al., 2011). In this issue, Cunningham and Skelly (2011) give a timely review on the role of prostaglandins in cognitive dysfunction and AD. They detail the function of prostanoid receptors and cyclooxygenase enzymes in CNS disorders and also explore recent research on inflammation in episodes of delirium.

The final articles in this special issue examine potential therapeutics for treatments of CNS disorders and assess the models used to test these drugs. Two articles examine *in vitro* findings for anti-inflammatory drugs in neurodegenerative diseases. Lee et al. (2011) use *Magnolia obovata*, known to have anti-inflammatory and anti-oxidant properties, to protect neuroblastoma cells from neurotoxicity and oxidative damage. Hu et al. (2011) found novel anti-inflammatory and neuroprotective effects of the anti-psychotic drug clozapine in neuron-glia cultures, which appeared to be driven by microglial inhibition. Turning to *in vivo* systems, O'Reilly and Lynch (2011) demonstrate that the PPARy agonist, rosiglitazone, reduces Aβ accumulation and improves memory function in a transgenic mouse model of AD. These studies present promising findings for new anti-inflammatory uses for old drugs and positive cognitive outcomes from anti-inflammatory and anti-oxidant treatment in AD models

While these results are encouraging, many further studies are needed to validate these effects in higher animal species before finally transitioning to clinical trials. Li et al. (2012) present a provocative paper testing the hypothesis that age itself is a critical factor in AD, missing from many animal models, and potentially responsible for discrepancies from animal to human drug studies. They compared effects of anti-Aβ antibody therapy in two transgenic mouse models of AD, middle-aged APP/PS1 and aged APP mice. While Aβ clearance was greater in the middle-aged APP/PS1 mice, only the aged APP mice showed significant brain microhemorrhages. Moreover, aged APP mice had greater infiltration of GFP-labeled monocytes into the CNS than middle-aged APP/PS1 mice despite having less amyloid than the latter. These findings stress the importance of using aged animal models of AD in preclinical studies for enhanced predictive power in later clinical trials.

We are excited to present this collection of timely articles to the readers of the *Journal of Neuroimmune Pharmacology*. As the average lifespan continues to increase and the population ages, issues of inflammation, aging, and cognitive function will become even more critical. Age is a key risk factor for many neurological disorders including AD, Parkinson's disease, and stroke—and the cognitive dysfunction in these diseases can be quite debilitating. The reviews, primary research articles, and brief reports presented here provide both in depth analysis of specific immune factors involved in memory impairments and chronic disease as well as a breadth of coverage on the role of inflammation in various disease models. We are grateful for the opportunity to extend the discussion we began at the Schmitt Symposium on Neuroinflammation in Chronic Disease and Aging and thank all the authors for their contributions to this discussion.

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