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REVIEW

NEUROINFLAMMATION IN THE NORMAL AGING HIPPOCAMPUS

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Abstract—A consequence of normal aging is a greater susceptibility to memory impairments following an immune challenge such as infection, surgery, or traumatic brain injury. The neuroinflammatory response, produced by these challenges results in increased and prolonged production of pro-inflammatory cytokines in the otherwise healthy aged brain. Here we discuss the mechanisms by which long-lasting elevations in pro-inflammatory cytokines in the hippocampus produce memory impairments. Sensitized microglia are a primary source of this exaggerated neuroinflammatory response and appear to be a hallmark of the normal aging brain. We review the current understanding of the causes and effects of normal aging-induced microglial sensitization, including dysregulations of the neuroendocrine system, potentiation of neuroinflammatory responses following an immune challenge, and the impairment of memories. We end with a discussion of therapeutic approaches to prevent these deleterious effects.

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Key words: normal aging, neuroinflammation, memory impairments, microglial priming, danger signals, neuroendocrine dysregulation.

Contents

INTRODUCTION

It has long been noted in the clinical literature that otherwise healthy aging individuals often suffer precipitous declines in cognitive abilities, including long-term memory function, following an inflammatory challenge such as an infection (Anttila, 1992; Craft et al., 2012), a surgery (Bedford, 1955; Ramaiah and Lam, 2009), or a head injury (McAllister, 1992; Tokutomi et al., 2008; Senathi-Raja et al., 2010). Importantly, these mild cognitive impairments have been shown to increase susceptibility to the development of dementia later in life (Alzheimer's Association, 2014). Notably, advanced age is the highest risk factor for suffering these mild cognitive impairments, as well as for developing dementia (Moller et al., 1998; Alzheimer's Association, 2014). With the first of the baby boomer generation now turning 65, by the year 2030, approximately 23% of the U.S. population will be over 65 (Wimo et al., 2013; Alzheimer's Association, 2014), a demographic phenomenon that has earned the term "silver tsunami" to characterize its magnitude. Because our unique memories are what make us individuals and give our lives meaning, insults that threaten to destroy already stored memories or disrupt our ability to form new memories can have devastating consequences. Caring for people with dementia in the U.S. has been

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Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; BDNF, brain-derived neurotrophic factor; CCI, controlled cortical impact; CD11b, complement receptor 3; CORT, corticosterone; ERK, extracellular signal-regulated protein kinase; GC, glucocorticoid; GLT1, glutamate transporter subtype 1; GR, glucocorticoid receptor; ICM, intra cisterna magna; IL-1RA, IL-1 receptor antagonist; IL-1β, interleukin-1 beta; IL-6, interleukin-6; JNK, c-jun N-terminal kinase; LPS, lipopolysaccharide; LTP, long-term potentiation; MAP, mitogen-activated protein; MHC II, major histocompatibility complex II; NLRP3, Nucleotide-binding domain, Leucine-Rich Repeat, Pyrin domain containing protein 3; POCD, post-operative cognitive decline; ROS, reactive oxygen species; TBI, traumatic brain injury; TNF-α, tumor necrosis factor-alpha.

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projected to cost $20 trillion over the next 40 years (Alzheimer's Association, 2014). Thus, in addition to the tremendous human suffering, the economic strain on the health care system and the federal budget is enormous. Therefore, scientific advances in the area of aging-related cognitive declines are of great and immediate importance. In this article, we will review the current literature related to hippocampal-dependent memory in normal aging and how it is negatively impacted by an inflammatory challenge. An important issue that merits attention here is the distinction between "normal" brain aging and "pathological" brain aging. Our work, as well as the preponderance of studies reviewed here, focuses on studying *normal* aging in which obvious neurodegeneration and senescence is not a prominent feature. Instead, older animals exhibit *primed* neuroinflammatory responses that require a secondary challenge for overt neuroinflammation or memory impairments to occur. A considerable amount of literature has also studied *senescent* animals, which exhibit *basal* behavioral and brain cytokine profiles dramatically different from those of younger animals, and whose brains are generally classified under the heading of "neurodegeneration" (Cacabelos et al., 1994; Luterman et al., 2000; Remarque et al., 2001). Neurodegeneration and the memory changes that depend on neurodegeneration are outside the scope of this review (see Fig. 1).

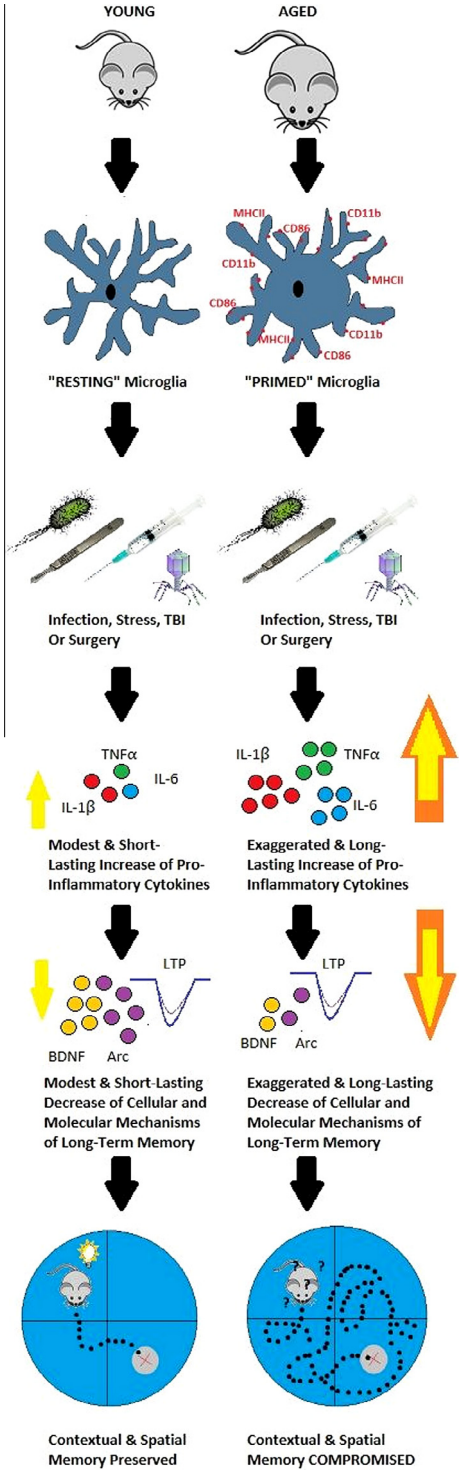

Fig. 1.

COMMUNICATION BETWEEN THE PERIPHERAL IMMUNE SYSTEM AND THE BRAIN

Before considering the literature concerning immune challenge-induced hippocampal memory impairments, it is critical to understand that there is extensive bi-directional communication between the immune system and the central nervous system. Infection or injury initiates a peripheral acute phase response that involves a cascade of local and systemic events. Interleukin-1 beta (IL-1β), a pro-inflammatory cytokine, is a principal player in this cascade. As part of its role in this response, IL-1β enhances T and B lymphocyte proliferation and stimulates natural killer cell cytocidal activity to eliminate the injured cells or invading pathogen. IL-1β also induces the production of other cytokines from many cell types such as tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), which in turn have secondary effects on other cells. Blood-borne and neural routes of communication between the peripheral and central nervous systems have been well defined over the last two decades (Dinarello et al., 1988; Ericsson et al., 1994; Goehler et al., 1997; Gaykema et al., 1998; Banks et al., 1999; Maier, 2003; Bachstetter et al., 2009). As a result of this communication, neural activity is altered quite dramatically during and following a peripheral immune challenge (Maier and Watkins, 1998; Maier, 2003), leading to de novo cytokine production within the brain parenchyma, with this response being driven primarily by activated microglial cells (Van Dam et al., 1995; Laye et al., 1996; Nguyen et al., 1998; Turrin et al., 2001). Conversely, acute and chronic brain injury induces significant cytokine and chemokine expression in the liver causing leukocyte recruitment, liver damage, as well as sickness and depressive-like behaviors (Campbell et al., 2003, 2005, 2007a), and blocking cytokine production in the periphery, modulates the central inflammatory response, and prevents some of the behavioral alterations (Campbell et al., 2007b; Jiang et al., 2008). As we will discuss in more detail in the sections that follow, microglial cells in

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