Neuroscience and Biobehavioral Reviews 75 (2017) 114–128

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions

Svetlana Di Benedetto[a,b], Ludmila Müller[a,*], Elisabeth Wenger[a], Sandra Düzel[a], Graham Pawelec[b]

[a] Max Planck Institute for Human Development, Center for Lifespan Psychology, Lentzeallee 94, 14195, Berlin, Germany
[b] Center for Medical Research, Department of Internal Medicine II, University of Tübingen, Waldhörnlestr. 22, 72072 Tübingen, Germany

ARTICLE INFO

Article history:
Received 2 December 2016
Received in revised form 24 January 2017
Accepted 30 January 2017
Available online 1 February 2017

Keywords:
Aging
Brain
Immunosenescence
Inflammaging
Neuroplasticity
Neuroinflammation
Cytokines
T cells
Microglia
Neurotrophic factors
Cognition
Physical exercise
Cognitive intervention

ABSTRACT

It is widely accepted that the brain and the immune system continuously interact during normal as well as pathological functioning. Human aging is commonly accompanied by low-grade inflammation in both the immune and central nervous systems, thought to contribute to many age-related diseases. This review of the current literature focuses first on the normal neuroimmune interactions occurring in the brain, which promote learning, memory and neuroplasticity. Further, we discuss the protective and dynamic role of barriers to neuroimmune interactions, which have become clearer with the recent discovery of the meningeal lymphatic system. Next, we consider age-related changes of the immune system and possible deleterious influences of immunosenescence and low-grade inflammation (inflammaging) on neurodegenerative processes in the normally aging brain. We survey the major immunomodulators and neuroregulators in the aging brain and their highly tuned dynamic and reciprocal interactions. Finally, we consider our current understanding of how physical activity, as well as a combination of physical and cognitive interventions, may mediate anti-inflammatory effects and thus positively impact brain aging.

Contents

* Corresponding author.
E-mail address: lmueller@mpib-berlin.mpg.de (L. Müller).

http://dx.doi.org/10.1016/j.neubiorev.2017.01.044
0149-7634/

1. Introduction

For many years the brain was considered as an immune-privileged space, functioning fully autonomically in isolation from the immune system, separated by a relatively impenetrable blood-brain barrier. However, recent findings are resulting in a radical shift in this view. First, it used to be believed that the brain has no lymphatic system, reflecting lack of entry of lymphocytes into this sensitive area. The appearance of immune cells in the brain was considered an exceptionally harmful pathological incident leading to neurodegeneration. Second, for many years, neurogenesis was thought to be restricted to embryonic and developmental stages, but this view is now also being revised following the discovery of adult neurogenesis. It is now well-accepted that the brain is plastic and actually capable of change throughout the lifespan, adapting its function to different external and internal demands by altering its structure (Lövdén et al., 2013). The term "neuroplasticity" encompasses the potential for a number of functional and structural mechanisms, regulated by diverse extrinsic and intrinsic cues, all of which allow neuronal remodeling, formation of novel synapses and birth of new neurons (Calabrese et al., 2014). The immune system actively participates in this process, and immune cells and their secreted mediators can modulate adult neurogenesis under both homeostatic conditions and in phases of remodeling (Aimone et al., 2014; Kempermann et al., 2002; Leiter et al., 2016; Singhal et al., 2014; Villeda et al., 2011; Yau et al., 2015; Yirmiya and Goshen, 2011; Ziv et al., 2006).

The central nervous system (CNS) is no longer considered as being restricted to limited interactions with the peripheral immune system. We now know that these two major physiological systems communicate with each other constantly and extensively through multiple pathways (Ellwardt et al., 2016; Quan and Banks, 2007). Recent technological advances allow us to address this crosstalk using such techniques as brain imaging, cell-specific targeting and sequencing. Animal models have additionally helped to shed light on the complex mechanisms of neuroimmune regulation (Berry et al., 2010; Capoccia et al., 2013; Veiga-Fernandes and Mucida, 2016). Scientific interest in these interactions has markedly increased since the discovery of a meningeal lymphatic system capable of carrying fluid, immune cells, and macromolecules from the CNS to the draining lymph nodes (Louveau et al., 2015; Raper et al., 2016).

It could be postulated that the immune system and CNS represent the two major adaptive systems of the body. In this context, chronic inflammation can be regarded as a result of the maladjustment of these two major adaptive systems to resolve acute inflammation, which in turn may affect the course of the aging process (Elenkov et al., 2005). The interplay between aging, genetic predisposition, and environmental exposures initiates systemic and local metabolic changes as well as inflammatory reactions that predispose an individual to neuropsychiatric and neurodegenerative diseases (Deleidi et al., 2015). Even conditions of the prenatal environment (such as maternal chronic stress) may have long-term consequences influencing postnatal development (Berry et al., 2015). Maternal obesity may already prove detrimental by providing an intrauterine environment with elevated glucocorticoids, insulin resistance and increased inflammation that influences fetal developmental pathways associated with unhealthy aging in later life (Hanson and Gluckman, 2014; Holvoet, 2012; Iozzo et al., 2014).

The focus of the present review is on neuroimmune interactions in "normal" aging, which have received relatively little attention, rather than neurodegenerative pathologies, which have been extensively reviewed recently (Da Mesquita et al., 2016; Feigenson et al., 2014; Goldeck et al., 2016; Hansel et al., 2010; Leza et al., 2015; Litteljohn et al., 2014; Na et al., 2014; Norden et al., 2015; Nunes et al., 2013; Swardfager et al., 2016; Tansey, 2010; Tansey and Goldberg, 2010; von Bernhardi et al., 2010). Thus, we summarize representative studies and reviews concerning the multitude of reciprocal and dynamic communications between the nervous and immune systems during normal aging, the systemic consequences of age-related dysfunction of these communications, and possible interventions to mitigate this process. First, we will introduce the neuroimmunomodulatory mechanisms involved in the process of learning and memory under normal conditions, and then discuss their dysregulation in aging.

2. Immune modulation of neuroplasticity

The immune system communicates constantly with the CNS and is involved in modulating behavior and in many other critical neurological functions throughout the lifespan (Wilson et al., 2002). Normal learning and memory processes are dependent on hippocampal neurogenesis and deficits in such processes may lead to impairments in both spatial and non-spatial learning tasks (Yau et al., 2015). It has been well established that hippocampal neurogenesis in the adult brain is regulated by various intrinsic and extrinsic mechanisms (Kempermann et al., 2002). One of the mechanisms for optimal hippocampal neurogenesis is dependent on the immune system, an unexpected finding first demonstrated in mice with severe combined immune deficiency (SCID mice) and in mice lacking certain immune cell populations (Brynskikh et al., 2008; Kipnis et al., 2004; Wolf et al., 2009; Ziv et al., 2006). The role of systemic immune cells in supporting brain function and plasticity has been demonstrated for hippocampus-dependent functions such as spatial memory and sensorimotor gating (Kipnis et al., 2004; Ron-Harel et al., 2011; Wolf et al., 2009). Remarkably, it was found that systemic depletion of $CD4^+$ T lymphocytes led to significantly reduced hippocampal neurogenesis, impaired reversal learning in the Morris water maze, and decreased brain-derived neurotrophic factor (BDNF) expression in the brain (Wolf et al., 2009). Repopulation with $CD4^+$ T cells restored the deficits observed in immune-deficient mice, highlighting the role of this T-cell population as being pro-neurogenic under physiological conditions (Leiter et al., 2016). Apparently, hippocampus-dependent cognitive ability is supported by CNS-specific T cells, which accumulate within the brain meningeal spaces and produce interleukin (IL)-4, inducing BDNF production (Fig. 1) during the performance of cognitive tasks (Derecki et al., 2010). $CD4^+$ T cells were shown to promote and maintain neurogenesis by positively influencing microglia and regulating insulin-growth factor (IGF)-1 transport into the brain, thereby also regulating BDNF levels (Wekerle, 2006; Ziv et al., 2006). CNS-specific $CD4^+$ T cells are thought to be stimulated by macrophages, which circulate through the brain parenchyma, phagocytizing and processing CNS-derived self-antigens, such as myelin and/or neural debris. They are able to present these processed antigens and to stimulate naïve T cells in the periphery, resulting in the development of CNS-specific memory T cells (Fig. 1, bottom left), which later appear in the meningeal cerebrospinal fluid (CSF). Here they can be re-stimulated by brain-surveying macrophages (Fig. 1, top left) to produce neuroprotective cytokines and neurotrophic factors, supporting normal cognitive performance, learning and memory (Ron-Harel et al., 2011). T cells found in the CSF are mostly of central memory phenotype, expressing CCR7, CD27 and the activation marker CD69 (Ellwardt et al., 2016), in contrast to those within the choroid plexus (CP), which appear to be of effector-memory type (Baruch and Schwartz, 2013). Cytokines secreted by T cells, such as IL-4 and transforming growth factor β (TGF-β), have a protective effect on neurons and neural precursor cells (Fig. 1, central). Additionally, IL-4 stimulates microglia to produce BDNF, IGF-1, TGF-β, which all influence neuronal functioning (Burch, 2014; Ellwardt et al., 2016). IL-4 also