Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2017 October 03; 79(Pt A): 49–57. doi:10.1016/j.pnpbp.2016.09.003.

Contributions of the adaptive immune system to mood regulation: mechanisms and pathways of neuroimmune interactions

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Abstract

Clinical and basic studies of functional interactions between adaptive immunity, affective states, and brain function are reviewed, and the neural, humoral, and cellular routes of bidirectional communication between the brain and the adaptive immune system are evaluated. In clinical studies of depressed populations, lymphocytes—the principal cells of the adaptive immune system—exhibit altered T cell subtype ratios and CD4⁺ helper T cell polarization profiles. In basic studies using psychological stress to model depression, T cell profiles are altered as well, consistent with stress effects conveyed by the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. Lymphocytes in turn have effects on behavior and CNS structure and function. CD4⁺ T cells in particular appear to modify affective behavior and rates of hippocampal dentate gyrus neurogenesis. These observations force the question of how such actions are carried out. CNS effects may occur via cellular and molecular mechanisms whereby effector memory T cells and the cytokine profiles they produce in the blood interact with the blood-brain barrier in ways that remain to be clarified. Understanding the mechanisms by which T cells polarize and interact with the brain to alter mood states is key to advances in the field, and may permit development of therapies that target cells in the periphery, thus bypassing problems associated with bioavailability of drugs within the brain.

Keywords

Neuroimmune; Lymphocytes; CD4⁺ T cells; Chronic stress; Depression; Blood brain barrier; Cytokines; IFN γ ; IL-4

1. Introduction

Converging evidence from multiple clinical and experimental lines of research supports a role for the peripheral immune system in the etiology and maintenance of depressive disorders. Support for this role is based on the following: 1) recent evidence from genome-

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wide association studies show prominent links between immune gene variants and mood disorders (Bufalino et al., 2013; Network and Pathway Analysis Subgroup of Psychiatric Genomics, 2015; Wong et al., 2008); 2) autoimmune diseases, infections, and other inflammatory diseases are comorbid with depression (Benros et al., 2013; Maes, 2011); 3) immune system molecules such as cytokines are elevated in depressed patients (Baumeister et al., 2014; Capuron and Dantzer, 2003; Dowlati et al., 2010; Dunn et al., 2005; Felger and Lotrich, 2013; Liu et al., 2012; Zunszain et al., 2013); 4) depression symptoms are induced following therapeutic administration of the cytokines interleukin-2 (IL-2) or interferon α (Raison et al., 2009); and 5) proinflammatory cytokines produce sickness behavior in animals that is reminiscent of depression by several criteria such as fatigue, anhedonia, changes in appetite, and sleep disturbances (Dantzer, 2012; Dantzer et al., 2008).

While there are excellent reviews on the subject of brain-immune interactions underlying psychiatric disorders (Haapakoski et al., 2016; Maier and Watkins, 1998; Najjar et al., 2013), we will focus more specifically on interactions between the brain and the adaptive immune system, which has only recently received attention in relation to mental health. The adaptive immune system is one of two functionally distinct arms of what is collectively called the peripheral immune system (Fig. 1). The first arm is the innate immune system, including monocytes and other cells of the myeloid lineage that rapidly respond to pathogenic challenges. The second arm is the adaptive immune system, comprising lymphocytes that exhibit a delayed response in the face of inflammatory challenge during which adaptation and commitment (polarization) of lymphocytes occur to generate cellular memory for pathogens.

2. Organization of pathways connecting the brain and the immune system

2.1. Brain-to-Immune Signaling

Appreciation of a functional link between the immune system and the central nervous system (CNS) requires some knowledge of how they are physically linked to achieve bidirectional communication. We begin with the brain, which communicates to immune organs such as the spleen, thymus, and lymph nodes via neural, humoral, and cellular pathways. Neural and humoral signaling mechanisms are fairly well characterized (Glaser and Kiecolt-Glaser, 2005; Irwin and Cole, 2011); briefly, efferent neural and humoral control of immune organs originates in the brain's stress circuits, which converge on autonomic control centers at the level of the hypothalamic paraventricular nucleus (PVN). Higher order neural circuits, largely limbic in nature, drive stress-related changes in PVN activity (Ulrich-Lai and Herman, 2009; Wrona, 2006). Some PVN neurons project to the spinal cord intermediolateral cell column to control the sympathetic preganglionic neurons. Other PVN neurons project to the median eminence and are the origin of the hypothalamic-pituitary-adrenal (HPA) axis, which—when activated—culminates in the release of glucocorticoid hormones into the blood. These efferent systems notify the periphery of threat (Ulrich-Lai and Herman, 2009). Prolonged HPA signaling is thought to be a key manifestation of life stress and depression (McEwen, 2004) and plays a major role in mediating effects on the immune axis (Pariante and Lightman, 2008).

Neural efferent signaling to the lymphoid organs is accomplished via noradrenergic innervation by the sympathetic nervous system (SNS). The other arm of the efferent peripheral autonomic nervous system, the parasympathetic system, does not innervate these organs (Nance and Sanders, 2007; Schafer et al., 1998), although a vagal “anti-inflammatory reflex” has been proposed wherein cholinergic parasympathetic efferent fibers end in the sympathetic celiac ganglion just proximal to lymphoid organs (Andersson and Tracey, 2012; Pavlov and Tracey, 2015). Norepinephrine is therefore the dominant neurotransmitter for brain-to-immune system neural communication. In addition, co-released neuropeptide Y (NPY), corticotropin releasing hormone (CRH), substance P, vasoactive intestinal polypeptide (VIP), and calcitonin gene-related peptide (CGRP) can all modulate the activity of immune cells (Elenkov et al., 2000; Miller et al., 1998; Steinman, 2004).

Within the immune organs, notably lymph nodes and spleen, neurotransmitters are released onto the two major lymphocyte cell types—T and B cells. Activated B cells generate the humoral immune response to extracellular pathogens by producing circulating antibodies that recognize specific epitopes. Activated T cells differentiate into either CD8⁺ T cytotoxic (killer) cells, which induce the death of infected cells, or one of several forms of CD4⁺ T helper cells, which “manage” the immune response by directing other cells to perform specific tasks. These CD4⁺ subtypes include T helper 1 (Th1), Th2, Th17, or Treg, each designed to eliminate different types of pathogens or promote self-recognition (Fig. 1). They are best identified by the prototypic cytokines they produce—proinflammatory interferon γ (IFN γ), anti-inflammatory IL-4, proinflammatory IL-17, and regulatory TGF β , respectively (Luckheeram et al., 2012).

Evidence shows that adrenergic stimulation of this milieu of lymphoid cells is largely immunosuppressive, with other complex actions. One notable consequence is an altered balance between lymphocytic CD4⁺ Th1 versus Th2 cell phenotypes. SNS activity inhibits Th1 and drives Th2 cytokine responses, though this is a simplified picture and depends on the duration of stimulation (Elenkov et al., 2000; Nance and Sanders, 2007). We later return to this concept, as an altered balance of Th1 to Th2 cell types is seen in some clinical studies of depression.

Humoral input to lymphoid organs primarily occurs via glucocorticoid secretion from the adrenal glands in response to activation by the HPA axis. Glucocorticoids such as cortisol in humans and corticosterone in rodents reach all immune organs and cells via the blood. They also reduce the Th1/Th2 ratio in CD4⁺ T cells (Calcagni and Elenkov, 2006) and may further mediate a suppressive effect on the adaptive immune system by reducing lymphocyte proliferation, antibody production, and response to infections (Batuman et al., 1990; Webster Marketon and Glaser, 2008).

The final route for brain-to-immune signaling is cellular, which has only recently been anatomically described. The cellular route is important for the adaptive immune system's response to antigen presenting cells (APCs) in the unhealthy brain. Specifically, presentation of CNS peptide fragments to lymphocytes by APCs may occur when dendritic cells—potent APCs—drain into the deep cervical lymph nodes and engage T cells there, leading to aberrant CNS-reactivity. Dendritic cells reside in the meninges and choroid plexus of normal

healthy brain and can interact with and present antigen to T cells in disease conditions (Anandasabapathy et al., 2011). Until recently, a path by which APCs might circulate through the brain and reach lymphatic vessels was unknown. However, dendritic cells in the brain's rostral migratory stream were described in 2014 (Mohammad et al., 2014), and lymphatic vessels which travel alongside the dural sinuses and drain into deep cervical lymph nodes were identified in 2015 (Aspelund et al., 2015; Louveau et al., 2015). Thus migration routes out of the brain via drainage through the cerebrospinal fluid (CSF)—a flow pathway thought to carry debris and perhaps APCs like dendritic cells, lymphocytes, and macrophages—and into the lymphatic vessels are now more completely understood (Iliff et al., 2015). This pathway may contribute to the dialog between the brain and the adaptive immune system in neurological disorders (Ellwardt et al., 2016); it is possible by extension that it contributes in stress disorders, although there is no knowledge to date supporting this hypothesis.

2.2. Immune-to-Brain Signaling

Information traveling in the reverse direction, i.e., immune-to-brain signaling, is also conveyed through neural, humoral, and cellular routes. The neural route proceeds via sympathetic afferents, whose cell bodies reside in the dorsal root ganglia, and parasympathetic afferents, whose cell bodies reside in the nodose ganglion. Sensory endings in tissues throughout the body, including the lymphoid organs (Nance and Sanders, 2007), are capable of carrying afferent, immune-related signals to the brain via the spinal cord (sympathetic) (Black, 2002) and vagus nerve (parasympathetic) (Berthoud and Neuhuber, 2000). The humoral route is achieved by the multitudinous secreted products of immune cells—e.g., cytokines, chemokines, and other factors—that travel in the blood to reach distant target organs. The cellular route is that which makes the immune system unique among systems—namely, its aptitude for cellular trafficking throughout the body in the performance of its duties.

The humoral and cellular routes thus make up the backbone of immune system action on the body. However, a considerable obstacle for feedback and influence on the brain is the blood-brain barrier (BBB), which effectively blocks the passive entry of cells and large molecules like cytokines into brain parenchyma. However, evidence shows that there are mechanisms at play allowing the BBB to be breached under both normal and pathological circumstances. A number of papers have reviewed the phenomenon of cellular BBB crossing (Engelhardt, 2006; Gorman, 2009; Quan and Banks, 2007; Ransohoff and Engelhardt, 2012; Wilson et al., 2010). Under normal conditions, dendritic cells and macrophages (McMenamin et al., 2003) reside in and patrol meningeal spaces, choroid plexus, and circumventricular organs where altered BBB conditions exist due to lack of tight junctions in the vascular endothelial cells (Schulz and Engelhardt, 2005). In disease states, entry at these locations is greatly accelerated, and movement into the brain parenchyma occurs. T cells are found under normal conditions at low concentrations in the brain (Hickey, 1999) and in the CSF where they perform surveillance functions (Ransohoff and Engelhardt, 2012). They may enter via the choroid plexus and cross directly from blood to ventricular CSF via the so-called blood-cerebrospinal fluid (BCSF) barrier, and from there move freely in the ventricles and subarachnoid spaces. Notably, immune cells within the CSF can secrete immune molecules

that will diffuse throughout the interconnected ventricular, cisternal, subarachnoid, perivascular, and intercellular spaces of the brain parenchyma, moving along characterized CSF flow pathways (Proescholdt et al., 2000).

The relative concentration of leukocytes (white blood cells) found circulating in ventricular CSF is low (approximately 1000-fold less concentrated compared to blood (Seabrook et al., 1998)). However, more than 90% of the leukocytes in the CSF of healthy brain are T cells, half of which are CD4⁺ T helper cells (Meeker et al., 2012; Ransohoff and Engelhardt, 2012). These CD4⁺ cells are predominately central memory T (T_{cm}) cells generated in secondary lymph organs prior to their entry into CSF (Kivisakk et al., 2003). Actions of lymphocytes in the brain in autoimmune and pathological disease states are well described, but their actions in stress and depressive states are barely known.

The BBB is an effective barrier to blood-borne cytokines as well, though some are transported in low concentrations across barrier cells that possess specific transporter molecules (Banks, 2015). In addition, barrier cells have cytokine receptors that can transduce inflammatory signals from the blood by producing and releasing cytokines, nitric oxide, and prostaglandins into the CSF or brain parenchyma (Quan and Banks, 2007). This mechanism has been used to explain how peripheral cytokines induce CNS-mediated fever and sickness behavior (Eskilsson et al., 2014; Saper et al., 2012), but it has not yet been studied with regard to depressive behavior.

3. Adaptive immunity in affective disorders

3.1. Clinical studies

Increased life stress is a predisposing factor for depression and anxiety (Phillips et al., 2015), and psychological triggers for depression may originate in the CNS stress pathways described above. It has been proposed that prolonged psychological stress via the HPA axis generates a peripheral inflammatory response, which can induce or intensify depression and other disease states (Black, 2002; Slavich and Irwin, 2014). However, to date, most research on such neuroimmune interactions in affective disorders has focused on the innate immune system (Irwin and Cole, 2011; Smith, 1991). Briefly summarized, it is suggested that proinflammatory cytokines produced by cells of the innate immune system travel through the blood and gain access to the brain via direct and transduced pathways, thereby inducing sickness behavior, which has features that are associated with and might lead to the development of major depression (Dantzer et al., 2008; Dowlati et al., 2010). Many genetic and/or epigenetic factors might predispose toward elevated cytokine levels, concomitantly heightening the potential for exacerbation of depressive symptoms via neuroimmune interactions (Slavich and Irwin, 2014).

Similarly, signs of an abnormally functioning adaptive immune system have been noted in the serum of depressed patients (Maes, 2011; Miller, 2010). For example, suppression of lymphocyte proliferation is a common finding in depression and may be attributed to high cortisol associated with psychological stress (Dobbin et al., 1991; Li et al., 2010). One meta-analysis reported dampened rates of lymphocyte proliferation and subtype-specific population changes in major depressive disorder (Herbert and Cohen, 1993)—a finding later

replicated in an independent meta-analysis using stricter statistical criteria (Zorrilla et al., 2001).

While only one study to date has identified B cell alterations in patient groups (Robertson et al., 2005), T cell anomalies have been shown in many studies. T cell activation, differentiation, and proliferation in particular seem to be altered in people experiencing depression or who have undergone chronic bouts of stress. One well-studied phenomenon has been the altered ratio of CD4⁺ to CD8⁺ T cell subtypes, with mixed results. For example, CD4⁺/CD8⁺ T cell ratio increases have been reported in depressed patients (Maes et al., 1992a; Maes et al., 1992b), replicated by meta-analysis data (Zorrilla et al., 2001). However, decreases in the CD4⁺/CD8⁺ ratio have also been found (Pavon et al., 2006). These discrepancies and other issues have been comprehensively addressed elsewhere (Maes, 2011), but the main problems with these studies are small sample size and subject heterogeneity. It is not evident what an imbalance in this ratio would portend for mood states.

Other groups have looked at CD4⁺ T cell polarization. For example, the ratio of helper CD4⁺ T cell subtypes Th1 and Th2 (Th1/Th2) was decreased in long-term caregivers, who represent a chronically stressed population (Glaser et al., 2001). Because alterations in the Th1/Th2 ratio can increase susceptibility to autoimmune diseases (Elenkov and Chrousos, 2002; Lorton and Bellinger, 2015) and cancer (Reiche et al., 2004), a more complete understanding of what impact this skewed ratio has on health is necessary. Importantly, antidepressants help restore the Th1/Th2 balance (Martino et al., 2012), suggesting a direct relationship between the Th1/Th2 ratio and depression. This finding may yield fruitful insight into what mechanisms could be manipulated for treatment.

3.2. Basic studies of chronic stress as a model of depression

3.2.1. Brain-to-immune actions of the adaptive immune system—The earliest work in the psychoneuroimmunology field showed that the adaptive immune system could be classically conditioned (Ader and Cohen, 1975); it was speculated that stress pathways from the brain to the immune system mediated this conditioning effect. Forty years later, studies have shown which specific lymphocyte subsets are affected (Pacheco-Lopez et al., 2009), and much more is known generally about stress effects on the immune system (Dhabhar, 2014). While many studies have demonstrated that acute stress and chronic stress differentially affect immunity (Dhabhar, 2009; Segerstrom and Miller, 2004), we will focus primarily on chronic stress because it is more strongly associated with depression (Phillips et al., 2015) and is known to suppress adaptive immunity—reducing lymphocyte proliferation and altering T cell subtype ratios and functionality (Bartolomucci, 2007; Dominguez-Gerpe and Rey-Mendez, 2001; Edgar et al., 2003; Frick et al., 2009a; Frick et al., 2009b; Schmidt et al., 2010; Silberman et al., 2004; Silberman et al., 2002). More recent studies showed that mice exposed to chronic mild stress had a decline in the Th1/Th2 ratio, extrapolated from relative changes in cytokine output, and a corresponding decline in cognitive performance on the Y-maze (Palumbo et al., 2012). These deficits were reversed through administration of the immunomodulatory drug glatiramer acetate (Copaxone), a “universal antigen” that weakly activates a wide spectrum of self-reactive T cells and confers neuroprotective effects

(Chen et al., 2015; Kipnis and Schwartz, 2002). Other studies of chronic stress in rodents also found altered cytokines in blood, reflective of a reduced Th1/Th2 ratio (Frick et al., 2009a; Himmerich et al., 2013; Hou et al., 2013); however, this profile was not always consistent (Schmidt et al., 2010; Voorhees et al., 2013). It is important to note that the cytokine profile observed from blood is a composite result of both adaptive and innate immune cell output, so meaningful conclusions about the relative contributions of each may not be possible.

3.2.3. Immune-to-brain actions of the adaptive immune system on affective behavior

—This comingling of products from the innate and adaptive immune systems complicates specific attribution to the adaptive immune system in the etiology of mood disorders. One way to meet this challenge is to selectively modify cellular components of the adaptive system and examine the subsequent effects on animal behavior. A powerful approach is to examine lymphopenic mice, which lack all or some kinds of lymphocytes depending on the exact genetic mutation inducing the loss. Severe combined immunodeficiency (SCID) mice cannot produce lymphocytes due to a VDJ recombinase defect (Bosma and Carroll, 1991). Rag1^{-/-} and Rag2^{-/-} mice, due to a mutation in the recombination activating gene (*Rag*), cannot make T or B cells (Mombaerts et al., 1992; Shinkai et al., 1992). Nude mice are athymic and lack T cells and some B cells (Pantelouris, 1968). TCRβ^{-/-}δ^{-/-} mice lack T cells but not B cells (Mombaerts et al., 1994).

In the earliest studies examining their affective behavior, Rag1^{-/-} mice were reported to have increased exploratory behavior and more center entries compared to wildtype mice in the open field test, indicative of a less anxious state at baseline (Cushman et al., 2003). They were found to be more anxious in another study (Rattazzi et al., 2013), and not different from control in a third (Marvar et al., 2012). By comparison, Rag2^{-/-} mice may not have basal differences in anxiety or depression (Scheinert et al., 2016), though this, too, isn't entirely clear (Wolf et al., 2009). Both Rag1^{-/-} and Rag2^{-/-} mice exhibited normal susceptibility to an anxiogenic restraint-stress (Marvar et al., 2012; Scheinert et al., 2016). Nude and SCID mice relative to strain-matched wildtype control mice both showed increased anxiety basally and failure to adapt to psychological stress (Cohen et al., 2006). In another study, SCID mice showed social interaction deficits but not increased anxiety compared to their C57BL/6 wildtype counterparts (Filiano et al., 2016). TCRβ^{-/-}δ^{-/-} mice had minor abnormalities in anxiety behavior that were sex-dependent (Rilett et al., 2015). Some of the conflicting data presented here may still be resolved by careful examination of a number of factors, such as strain and age of animals, nature of the task, and microbiota differences that might be related to standards of cleanliness in the facilities housing these immune-compromised animals.

Another method to assess the influence of adaptive immunity on behavior is to deplete specific cell types by administering antibodies systemically in wildtype animals. Kim et al. (2012) showed that depleting Treg cells by administering an anti-CD25 antibody increased anxiety-like behavior in the elevated-plus maze, suggesting that Treg cells are anxiolytic, though an alternate depletion strategy gave the opposite result (Cohen et al., 2006). In another recent study, when Treg cells were depleted by anti-CD25 antibody, restorative effects of bacterial immunization on anxiety behavior were blocked (Reber et al., 2016). In a

final example, CD4⁺ T cell depletion caused impairments in the Morris water maze, a hippocampal-dependent cognitive task, suggesting that CD4⁺ T cells support learning and memory. B cell depletion had no appreciable effect (Wolf et al., 2009).

Replacing cells of a particular type into a lymphopenic host—a process referred to as adoptive transfer—has yielded the most informative insights. This involves injecting cells of a known type into a lymphopenic host, causing homeostatic repopulation of the deficient lymphoid compartments (Min et al., 2004; Rocha et al., 1989). Cells from lymph nodes and spleen from wildtype mice transferred into SCID mice reversed the social deficits they had displayed in the social interaction task (Filiano et al., 2016). CD4⁺ T cells transferred into Rag2^{-/-} mice conferred antidepressant effects but also enhanced fear memory (Clark et al., 2016). Another CD4⁺ T cell subtype, Th17, which is notably pro-inflammatory through its production of IL-17, was examined in a model that did not use lymphopenic mice. As might be expected, T cells programmed to have a Th17 phenotype and injected into wildtype C57BL/6 mice were pro-depressive (Beurel et al., 2013). These data point to CD4⁺ T cells as the main cell type mediating normal affective behavior in mice (see also (Rattazzi et al., 2013)).

Basic tenets in immunology assert that T-cell memory is acquired as a result of antigen presentation by an APC, and it has long been held that antigen-dependent memory was required in T cells in order for them to exert beneficial influences on the CNS function. Michal Schwartz and her group at the Weizmann Institute of Science did seminal work exploring immune-to-brain actions of the adaptive immune system using lymphopenic mice. This group pioneered the notion that T cells can be beneficial to repair in various conditions, e.g., aging, spinal cord injury, and Alzheimer's disease (Baruch et al., 2013; Baruch and Schwartz, 2013; Schwartz and Shechter, 2010). Work from her lab demonstrated that lymphopenic mice adoptively transferred with CNS-autoreactive T cells, programmed to be effector memory T cells *in vitro* by immunization with myelin basic protein (MBP), performed better in spatial learning tasks and had higher rates of hippocampal neurogenesis than either wildtype control mice or mice given lymphocytes raised against a non-CNS-reactive epitope (Ziv et al., 2006). The CNS-reactive T cells also improved stress resilience after adoptive transfer (Cohen et al., 2006).

However, work from other groups, notably Kempermann's (Wolf et al., 2009), suggested that CNS-autoreactivity was not necessary for efficacy of transferred cells in supporting cognitive function and normal rates of neurogenesis. Supporting this notion, recent data showed that antigen-independent immunological memory could be maintained in CD4⁺ T cells by repetitive stressors of various kinds (Wang et al., 2015). Therefore, it is possible that T cells can be "educated" in the context of antigen-free chronic stress to exert effects on target organs, including the brain. The novel hypothesis that stress can somehow program lymphocytes to boost their efficacy in mood states has been investigated recently. We showed that adoptive transfer of lymphocytes from socially defeated but not from unstressed control mice conferred antidepressant-like and anxiolytic effects in both naïve (Brachman et al., 2015) and chronically stressed Rag2^{-/-} mice (Scheinert et al., 2016). The findings suggest that T cells retain memory for prior stressful life events, perhaps in order to restore

homeostasis in the host animal, and thus when transferred to an experience-naïve host confer therapeutic effects.

3.2.4. Hippocampal neurogenesis is a readout of immune-to-brain actions—

Adult hippocampal neurogenesis has proven to be a very instructive measure in studies of neuroimmune influence on brain function, especially hippocampal-dependent functions like certain aspects of cognition and affect. In the realm of affect, the hippocampus is a key neuroendocrine waystation, able to respond to stress feedback via glucocorticoids and subsequently modulate HPA activity. Importantly, rates of neurogenesis in the hippocampal dentate gyrus (DG) are reduced by stress and immune challenges (Dranovsky and Hen, 2006). Moreover, neurogenesis in the DG is not only extremely sensitive to environmental cues, it is also required for the manifestation of certain negative and positive behavioral outcomes (Leuner and Gould, 2010).

The relationship of the adaptive immune system to neurogenesis in the DG was demonstrated with a surprising, non-hypothesis-driven approach. Huang et al. (2010) used the quantitative trait loci (QTL) method to determine what genetic factors alter rates of neurogenesis in a variety of mouse strains. They found a significant correlation between DG proliferation rates and CD4⁺/CD8⁺ T cell ratios. The strongest QTL effect was associated with a gene governing selection and survival of CD4⁺ T cells, suggesting that CD4⁺ T cells somehow affect rates of neurogenesis. They tested that hypothesis using adoptive transfer in lymphopenic mice and demonstrated that Rag1^{-/-} mice and TCRα^{-/-} mice lacking T cells had reduced numbers of Ki67-positive newborn cells in the DG compared to strain-matched control mice. They next showed that CD4⁺, but not CD8⁺, T cell transfer restored levels of Ki67-positive cells in TCRα^{-/-} mice, in support of their hypothesis. These data together with other studies showing decreased neurogenesis in lymphopenic Rag1^{-/-}, SCID, and nude mice (Wolf et al., 2009; Ziv et al., 2006) suggest that some aspects of T cell function are required for normal maintenance of new-cell proliferation and survival in the hippocampal DG.

Because it is known that mood state correlates with rates of neurogenesis, both factors were examined in several studies of T cell function. Indeed, following lymphocyte transfer, rates of new cell proliferation in the DG were positively correlated with either improved mood states or increased cognitive performance (Brachman et al., 2015; Wolf et al., 2009; Ziv et al., 2006). These data support an apparently crucial role for the hippocampus in neuroimmune interactions and further suggest that the hippocampus is a target for molecular factors that link the adaptive immune system with CNS circuits controlling mood states.

4. Mechanisms of immune-to-brain influence

How do adaptive immune cells and their humoral products alter brain function, leading to changes in affective behavior and hippocampal neurogenesis? To our knowledge, nothing is known about the neural route in this regard, but the humoral and cellular routes have been investigated.

4.1. Humoral routes

There are clear examples in the literature demonstrating that circulating molecules of the immune system exert influence on brain and behavior. In one striking study, blood exchange by parabiosis between young and old animals was capable of reversing age effects on cognition and hippocampal function (Villeda et al., 2011). In that model, chemokines were thought to be important, but it was not known how they gained access to the brain. In stress studies, circulating IFN γ and IL-4—products of Th1 and Th2 T helper cells, respectively—have been carefully considered. One study reported that chronic mild stress induced a decreased ratio of IFN γ levels relative to IL-4 in lymph nodes, and this correlated with a reduction in spatial learning and DG neurogenesis (Palumbo et al., 2012). Interestingly, an *in vitro* assay showed that IFN γ enhanced neurogenesis and IL-4 enhanced gliogenesis of newborn neurons (Butovsky et al., 2006), and IFN γ overexpressing transgenic mice had elevated DG neurogenesis (Baron et al., 2008). Recalling that chronic stress reduces Th1 and increases Th2, it becomes possible to suggest that stress exerts its effect through the adaptive immune system by decreasing IFN γ and increasing IL-4, thereby directing DG cell production towards gliogenesis and away from neurogenesis.

Though the exact mechanism by which humoral products such as IFN γ and IL-4 act on neurons remains uncertain, it may occur directly by cytokine action on neurons that bear the appropriate receptors (Filiano et al., 2016) or indirectly through microglia (Butovsky et al., 2006). Microglia are good candidates as they are richly endowed with cytokine receptors (Kettenmann et al., 2011) and have several mechanisms by which they can interact with neurons. Microglia can be polarized into M1-like and M2-like activation states (Cherry et al., 2014; Edwards et al., 2006). M1 is proinflammatory and may promote psychiatric disorders (Nakagawa and Chiba, 2014) whereas M2 is anti-inflammatory and was associated with elevations in cognition, mood, and neurogenesis in animal inflammation models (Brachman et al., 2015; Yang et al., 2016). Microglia can also facilitate neuronal changes like synaptic plasticity via production of brain-derived neurotrophic factor (BDNF) (Parkhurst et al., 2013). In many studies, BDNF levels correlate with behavioral outcomes, both positive and negative, suggesting that production of this neurotrophin may be a CNS mediator of the peripheral actions of lymphocytes (Chen et al., 2015; Derecki et al., 2010; Wolf et al., 2009; Yang et al., 2016; Ziv et al., 2006). However, BDNF production levels in cultured microglia were not altered in response to cultured media derived from Th1- or Th2-cell lines (Seguin et al., 2003). Thus the mechanisms by which BDNF might respond to peripheral immune stimuli and contribute to CNS effects are unclear and may involve intermediary pathways. As a cautionary note regarding BDNF data, until perhaps recently (Chacon-Fernandez et al., 2016), there have not been good BDNF antibodies that mark the protein selectively, and thus, findings—especially by immunohistochemistry—should be interpreted with caution.

4.3. Cellular routes

How might T cells get across the BBB, and do they migrate into the brain parenchyma when induced by stress? Leukocytes—dendritic cells, macrophages, and lymphocytes—routinely patrol the brain by established routes of entry and egress across the BBB (Ousman and Kubes, 2012; Ransohoff et al., 2003). The choroid plexus is a well-described gateway for

leukocyte trafficking into the brain, with direct access to the ventricular CSF (Baruch and Schwartz, 2013; Herkenham, 2005; Sallusto et al., 2012). The Schwartz group has greatly expanded our understanding of T cell trafficking through the choroid plexus in chronic inflammation and aging models (Baruch et al., 2014; Baruch et al., 2015a; Baruch et al., 2013; Baruch et al., 2015b; Baruch and Schwartz, 2013). This group has also shown that acute exposure to predator odor stress caused a modest increase in lymphocyte trafficking into the choroid plexus (Lewitus et al., 2008).

Recent work has shifted emphasis from the choroid plexus to the meninges; Kipnis' group in particular has made several observations of lymphocytic residence in this compartment (Derecki et al., 2010; Filiano et al., 2016; Radjavi et al., 2014a; Radjavi et al., 2014b). In early publications, they proposed that T cells in the meninges secrete IL-4 into the CSF of the subarachnoid spaces; once there it can diffuse to key target sites and alter neuronal function (Gadani et al., 2012). In one study, mice tested in the Morris water maze had increased numbers of IL-4 producing Th2 cells in the meninges. Blocking this T cell accumulation or eliminating IL-4 led to the conclusion that IL-4 is a key molecule responsible for supporting cognitive performance and DG neurogenesis (Derecki et al., 2010). In a more recent publication, they proposed that meningeal T cells produce IFN γ , which diffuses into superficial layers of cerebral cortex and acts on inhibitory neurons that bear IFN γ receptors, importantly with the resulting effect on prefrontal cortical circuitry of restoring a balance in circuits that drive affective behavior (Filiano et al., 2016). They concluded from an exhaustive set of experiments that meningeal T cell-derived IFN γ serves a normal and meaningful evolutionary role in promoting social affiliation.

The apparent restriction of T cells to the meninges and other BBB havens is consistent with the fact that there is no known antigen presentation by APCs normally or following non-injurious behavioral manipulations such as psychosocial stress exposure. In contrast, studies of autoimmune disorders, neurodegeneration, and multiple sclerosis involve antigen presentation and extravasation of effector T cells into the brain parenchyma (Bartholomaeus et al., 2009; Ellwardt et al., 2016; Goverman, 2009; Schlager et al., 2016), described thoroughly elsewhere (Engelhardt, 2006; Wilson et al., 2010).

A vivid *in vivo* demonstration of T cell residence in the brain following adoptive transfer of green fluorescent protein (GFP)-positive lymph node cells in Rag2^{-/-} mice was recently published (Song et al., 2016). As expected, several weeks after repopulation into a naïve mouse, fluorescent lymphocytes were found scattered within the meninges, choroid plexus, and the circumventricular organs. Labeled cells within brain parenchyma were scarce and were largely confined to perivascular spaces (Song et al., 2016). Importantly, lymphocytes were not reported in the hippocampal vascular niche that supports DG neurogenesis (Palmer et al., 2000) in this or any other study to date.

A recent study found a relatively high (compared to spleen) proportion of Treg T cells in unperturbed rat brain, assayed by flow cytometry of cells from dissected cerebral cortical tissue (Xie et al., 2015). However, another group using the same technique found virtually no T cells or B cells within the non-manipulated brain (Silverberg et al., 2010), and the prevailing dogma is that parenchymal infiltration does not occur under normal conditions

(Herz et al., 2011). It will be important to rule out contamination by the meninges in studies reporting recovery of significant T cell numbers from the brain.

Future studies will determine whether the composition, degree, and spatial distribution of lymphocytes in brain are altered by stress. The possibility remains, however, that lymphocytes and their secreted products can exert paracrine influences from locations in and around the CSF-filled compartments where they reside. From this perspective, knowledge of CSF flow pathways through the brain is valuable (Proescholdt et al., 2000).

4.4. Other routes

A final and exciting possibility for T cell influence on brain is through exosome shedding. Exosomes are nano-sized vesicles that are shed by immune cells (Denzer et al., 2000; They et al., 2009). In one study, activated T cells released exosomes, which in turn activated neighboring, naïve T cells (Wahlgren et al., 2012). Exosomes can cross the BBB and are being considered as a therapeutic delivery vehicle for neurological diseases (Hu et al., 2012; Wood et al., 2011). In particular, their tendency to package and release microRNAs may be significant for their function (de Candia et al., 2014). Exosomes and microRNAs may contribute to the neuroimmune component of depression (Brites and Fernandes, 2015).

5. Therapeutic considerations

Bidirectional communication between the brain and the immune system has received much attention because of the potential for understanding neuropsychiatric diseases and developing new therapies to treat them. For example, changes in peripheral immunity have potential diagnostic value. Blood-based assays for depression designed to examine T cell population shifts are highly feasible and should be considered for clinical studies. For treatment, one approach specifically aimed at the adaptive immune system might be to program T cells by vaccinating patients with CNS antigens to promote therapeutic outcomes (Kipnis et al., 2004). Another objective might be to restore the disrupted Th1/Th2 balance observed in depressed patients (Song et al., 2009).

The demonstrated relationship between elevated cytokine levels in subsets of depressed patients inspired clinical trials targeting both arms of the immune system, i.e., with anti-inflammatory drugs, and this has generated some encouraging preliminary results (Muller et al., 2006; Najjar et al., 2013; Raison et al., 2013). One clear advantage that can be exploited by targeting the peripheral immune system of depressed patients is the obviation of drug delivery across the BBB; this has heretofore been a formidable challenge for some pharmacological manipulations.

Finally, immunotherapy approaches based on targeted “adoptive cell therapy” have been successfully applied to certain types of cancer by Steven Rosenberg’s laboratory, and early results are encouraging (Restifo et al., 2012; Rosenberg and Restifo, 2015). Briefly, cells taken from a patient’s tumor are grown in culture; the patient’s T cells are then tested for reactivity to tumor-specific antigens. Reactive cells are expanded and reinfused back into the patient following chemically induced lymphodepletion. This approach theoretically could be adapted to treatment-resistant depressive disorders that have otherwise failed to respond to

conventional anti-depressants. For example, lymphocytes taken from patients could be programmed towards Th1, Th2, or Treg polarities *in vitro* by standard expansion in culture (Walker et al., 1987). Adoptive transfer data suggest that depletion of Th17 cells or transfer of CD4⁺ cells, Treg cells, or “stress-educated” T cells may confer therapeutic value in the treatment of affective disorders.

6. Summary and future directions

The full extents of both the relationship and the mechanism of communication between the brain and immune compartments are unknown. We now know that the adaptive immune system affects hippocampal neurogenesis, mood, cognition, and may contribute to psychiatric dysfunction and mental disease. Despite an important role in supporting normal brain function, the adaptive immune system is the least well-understood component of neuroimmune signaling. A major contributor in this system appears to be the CD4⁺ T cell, though contributions of other lymphocyte cell types need to be explored. There is an urgent need for more basic research elucidating what conditions allow for T cell-acquisition of CNS memory in non-pathogenic conditions such as stress. Given the bidirectional communication endemic to the neuroimmune axis, interventions at any point in the afferent and efferent pathways might prove to have therapeutic value.

Acknowledgments

The work was supported by the NIMH Intramural Research Program, ZIA MH001090.

Abbreviations

APCs	Antigen presenting cells
BBB	blood-brain barrier
BDNF	brain derived neurotropic factor
CNS	central nervous system
CSF	cerebrospinal fluid
CRH	corticotropin releasing hormone
DG	dentate gyrus
HPA	hypothalamic pituitary adrenal
IFNγ	interferon γ
IL	interleukin
MBP	myelin basic protein
PVN	paraventricular nucleus
SCID	severe combined immunodeficiency

SNS	sympathetic nervous system
Tcm	T cells, central memory
Treg	T regulatory cell
TGFβ	transforming growth factor β

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Highlights

- The review focuses on the adaptive arm of the immune system
- Communication routes between the brain and immune organs are summarized
- Chronic stress and depression alter lymphocyte function in complex ways
- T lymphocytes have effects on mood and hippocampal neurogenesis
- Humoral and cellular actions at the blood-brain barrier are discussed

Fig. 1.

Innate and adaptive immune cells, derived from myeloid and lymphoid progenitors, which themselves originate from hematopoietic stem cells, facilitate the body's reaction to infection or damage. The innate immune system acts as a 'first-responder' to immediately curb a peripheral threat. It consists of granulocytes (i.e., basophils, neutrophils, and eosinophils), mast cells, lymphoid-derived natural killer cells, and monocytes which when activated primarily become macrophages. Antigen presenting dendritic cells can also form from monocytes, though multiple cell types appear to contribute to the dendritic cell population. The adaptive immune system acts more slowly, over the course of days or weeks, by developing cellular memory for pathogens. It consists of CD3⁺ T cells, which upon activation differentiate into CD8⁺ cytotoxic T cells or CD4⁺ T helper cells, and antibody-producing B cells. CD4⁺ T cells further subdivide into various T helper cell subtypes, including Th1, Th2, Th17, Treg, and others; they are primarily classified based on the prototypical cytokines they produce.