Is Central Nervous System an Immune-Privileged Site?

Shrestha R,[1,2,5] Millington O,[3] Brewer J,[4] Bushell T[5]

[1]Department of Pharmacology

Dhulikhel Hospital-Kathmandu University Hospital

Kathmandu University School of Medical Sciences
Dhulikhel, Kavre, Nepal

[2]Lilly Research Centre, Eli Lilly and Company, Surrey, UK

[3]Centre of Biophotonics, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

[4]Institute of Infection, Immunity and Inflammation College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

[5]Centre for Neuroscience, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

Corresponding Author

Rajeev Shrestha

Department of Pharmacology

Dhulikhel Hospital-Kathmandu University Hospital

Kathmandu University School of Medical Sciences
Dhulikhel, kavre, Nepal

E-mail: rmaleku@hotmail.com

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ABSTRACT

The central nervous system (CNS) was once considered to be an immune-privileged area. However, increasing evidence shows that the central nervous system is not an immune-privileged but is an active surveillance site. There is a bi-directional communication between the central nervous system and immune system. Normally, immune cells migrate into the central nervous system microenvironment through choroid plexus and interact with the central nervous system resident cells through either through neuromediators or immunomediators. This finding has led to a significant interest in neuroimmunological interactions and investigation onto the role of the immune system in the pathology of various neurological disorders and examine whether it can be targeted to produce novel therapeutic strategies.

KEYWORDS

Central nervous system, immune-privileged, blood-brain barrier, immune cells and lymphocytes

INTRODUCTION

The central nervous system (CNS) is a complex organ system consisting of billions of neurons that relay information via many billions of synapses. The immense capacity and ability to remodel itself in response to experience and the environment always fascinate neuroscientists, who believe that this organ is the most complicated machine ever known to the universe. The ability to receive, retain, recall and analyze complex information is a wonderful capacity of the nervous system.[1]

Whether or not the CNS is an immune-privileged site has been an intense debate among neuroscientists. The concept of an immuno-privileged site was first highlighted when allografts in eye and brain tissue were better persisted in comparison to other peripheral tissues.[2,3] These studies demonstrated that the graft showed little rejection in comparison to other parts of the body. On the other hand, proper neuronal function demands a tight regulation of the CNS microenvironment including concentration of different ions and other noxious substances.[4] For this proper control and the normal function of the CNS, the blood brain barrier (BBB) plays an important role.[5]

The BBB lies at the interface of the blood and the brain tissue that comprises microvascular endothelium, astrocytes, basement-membrane and pericytes.[6,7] To address the collective terms for the constituents of the BBB, the concept of a 'neurovascular unit' was proposed to emphasize more for the structure and function of BBB

integrity.[4,5] This unit protects the CNS from fluctuations of nutrients, hormones, metabolites and blood constituents including endogenous and exogenous compounds.[4,8] The endothelial cells of the BBB have distinct morphological and physiological properties in comparison to other endothelial cells of the body.[5,6,9] These endothelial cells lack fenestration with a tight junction reducing permeability to intercellular pathways and they express very low numbers of non-specific transporters.[6,9,10] Moreover, the highly polarized receptors and transporter systems play an important role in the movement of nutrients into the CNS and the efflux of metabolites or toxic substances into the vascular compartment.[5,10,11] Furthermore, it has also been suggested that pericytes play a major role in maintaining the BBB tight junction along with these endothelial cells.[12,13] An in vivo imaging study of mice lacking pericytes showed an increase in the permeability of the BBB to water as well as low-molecular and high-molecular mass tracers.[12]

Hence, the presence of a neurovascular unit, lack of conventional lymphatic vessels and limited parenchymal expression of major histocompatibility complex (MHC) molecules in the CNS along with the limited rejection of allografts in the CNS might have led us to consider the CNS as a immunologically privileged area.[14] However, it is now well accepted that the brain can no longer be considered immune-privileged. There is increasing evidence for the regular communication between the CNS and the immune system.[15-17] Research has shown that immune cells can enter the CNS via the choroid-plexus and reside in perivascular spaces or move into the neuropil.[18-21] Furthermore, it has been shown that the extravasation of these immune cells into the CNS involves a very complex set of adhesion molecules present on the endothelial cells and on the cell surface of these immune cells.[20-23] Common adhesion molecules that have been suggested to be involved in the extravasation of leukocytes include the intracellular adhesion molecule (ICAM) family, vascular cell adhesion molecule (VCAM), integrins, selectins and the junctional adhesion molecule (JAM) family.[7,14,24-26] Hence, this evidence suggests that the CNS is not an immunologically privileged area. Nevertheless, it is also true that the CNS is a more immunologically privileged site relative to other organs due to the presence of the BBB and tightly regulated immune response including limited movement of immune cells and expression of death ligand.[5,27]

Communication between central nervous system and immune system

Brain modulation of immune function

The most common way of communication is via humoral factors such as cortisol and epinephrine released from the hypothalamic-pituitary-adrenal (HPA) axis in response to stress with a stressor being anything that stimulates the activation of HPA axis and sympathetic nervous system.[17,28-30] Stress can alter antibody secretions as well as the release of pro-inflammatory as well as anti-inflammatory mediators.[31] Most immune cells express receptors for one or more hormones associated with HPA and sympathetic-adrenal-medullary axis and these hormones can regulate immune function via these receptors such as inhibition of inflammation and shifting production of cytokines from Th-1 cells to Th-2 cells, trafficking cells from lymph node to peripheral blood, increasing cytokine production and maintaining competence of immune cells including T cells, B cells and macrophages.[29,32-36] It has also been demonstrated that mice fail to recover from experimental autoimmune encephalomyelitis (EAE) after adrenalectomy , which suggests that the HPA axis plays a crucial role in modulation of the immune system as inflammation is known to be critically involved in the progression of this animal model of Multiple sclerosis (MS).[37] Moreover, nerve fibres present in the lymphoid organs also suggest a bi-directional communication between the CNS and immune system. Recently, it has been demonstrated that stimulation of vagus nerve fibres causes acetylcholine release from spleenic T cells.[38] These nerve fibres act as a link between these two systems which relay or receive signals and affect the physiological functions (such as antibody secretion and cytokines and chemokines release) of the immune cells.[38-40]

Immune regulation of brain function

Whilst it is clear that the CNS can influence immunity, the immune system also plays a crucial role in normal brain development, neuronal differentiation and synaptic plasticity.[41,42] Furthermore, various cytokines and chemokines are able to regulate secretion of neurotransmitters in the CNS , with interferons being the first cytokines identified to have an effect on neuronal function.[28,43-47] Cytokines can induce sickness behaviour (characterised by fever, reduction in activity and weight loss) and also regulate neuroendocrine effects, including release of different hormones.[48,49] Moreover, cytokines including interleukin (IL)-1, IL-2 and IL-6 are also found to regulate neuronal functions.[28,39,46] IL-1 and IL-6 stimulate HPA axis in secretion of corticotrophin-releasing hormones, whereas IL-2 can act as a neuroregulatory cytokine in the CNS.[28,46,50,51] IL-2 can affect the growth and survival of neurites, proliferation and maturation of oligodendrocytes, growth of microglia and also has effect on behaviour and electrocorticogram spectrum.[52-55] It has also been shown that systemic immunisation in mice caused a decrease in neurotransmitter levels in specific regions of the brain such as hypothalamus, hippocampus, locus coeruleus, supraoptic nucleus and paraventricular nucleus while causing an increase in the nucleus tractus solitarius.[44,56,57] From these studies, it is evident that the CNS and the immune system communicate with each other via various mediators. Furthermore, there are also several studies showing a direct interaction between cells of the CNS and cells of the immune system.[58-60] These immune cells are regularly patrolling the CNS and scanning for their cognate antigens in healthy as well as in diseased models like EAE.[19,24,61,62] Details of their movement and functions are dealt with in the sections below.

Movement of lymphocytes in and out of the CNS

As discussed above, there is a continuous communication between the CNS and the immune system either via various neuromediators / immunomediators or direct cell to cell interactions. In direct cell to cell interactions, immune cells especially leukocytes migrate into the CNS. Three pathways have been proposed for leukocytes movement to and from the CNS: i) from blood to cerebro-spinal fluid (CSF) across the choroids plexus (the site of the blood-CSF barrier), ii) from blood to subarachnoid space at the pial surface of the brain and iii) from blood to parenchymal perivascular space.[63] The first two pathways seem to be the most relevant under normal physiological conditions [64] whereas extravasation by the third pathway occurs only during an inflammatory event.[19,65-67] Normally, lymphocytes (predominantly T lymphocytes) migrate through the fenestrated endothelium of the choroid plexus stroma, interact with epithelial cells of the choroid plexus and enter the CSF at its site of formation.[63,68,69] It is known that activated T cells express specific chemokine receptors which enable them to interact with adhesion molecules expressed in the vascular endothelium.[14,70,71] In this process, only activated lymphocytes can undergo this extravasation event, independent of antigen specificity as these cells express chemokine receptors which help in this extravasation.[14,20,22,25,72] This process of extravasation requires defined interactions between molecules expressed in lymphocytes and endothelial cells of the BBB. These discrete steps include interaction between selectins and their ligands, integrins and cell adhesion molecules (CAMs), chemokines and their receptors, matrix metalloproteinase (MMPs) and their tissue inhibitors (TIMPs).

The initial contact between a leukocyte and an endothelial cell is referred to as 'tethering' and subsequent interactions are referred to as 'rolling' occur in the peripheral high endothelial venules (Fig 1A). These initial events of leukocyte recruitment are primarily mediated by the interaction between P-selectin glycoprotein ligand-1 (PSGL-1; expressed by all lymphocytes) and selectins. However, the role of endothelial P-selectin in recruiting lymphocytes into the CNS is still controversial. Although, some studies have suggested that P-selectin has a crucial role in the early migration of lymphocytes into the non-inflamed brain, others have suggested that there is no role of P-selectin in the migration of lymphocytes during inflammatory condition within CNS since P-selectin deficient mice also develop EAE which is indistinguishable from wild-type.[64,68,73,74,76-78] The 'rolling' of lymphocytes is followed by the interaction of α4β1 molecule (α4-integrin) expressed in the membrane of lymphocytes with vascular cell adhesion molecule (VCAM)-1 expressed on the endothelial surface which causes the capture of these lymphocytes.[23,79] This capturing process allows lymphocytes a sufficient time to interact with chemokine ligands (CCL19 and CCL21) expressed on the endothelial surface and leads to the activation as well as migration of lymphocytes into the

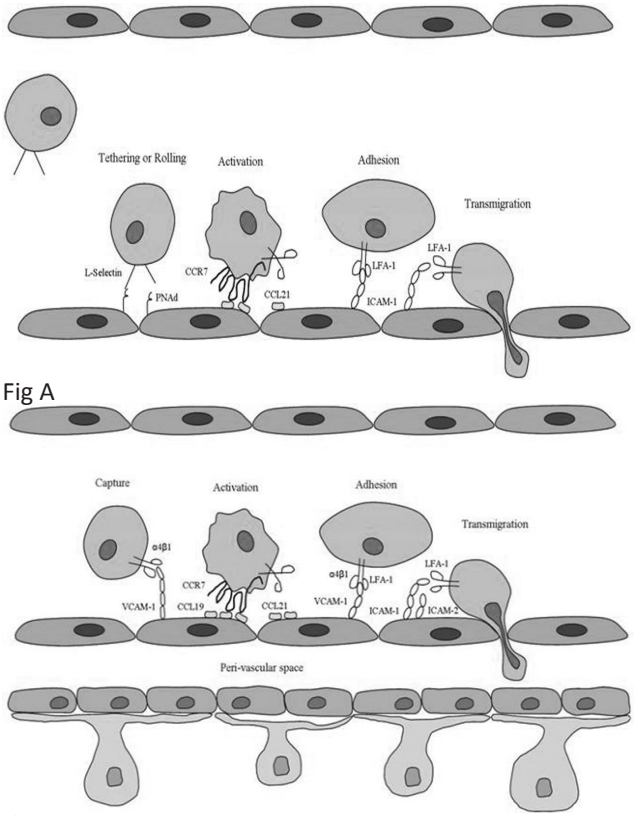

Fig A

Fig B

Figure 1. Schematic showing the multistep model of lymphcytes movement in two different compartments. (A) In the peripheral vascular endothelium, the extravasation of lymphocyte starts with tethering or rolling followed by activation, adhesion and transmigration.(B) At the endothelium of spinal cord, the extravasation of lymphocyte starts with direct capture without tethering or rolling and followed by activation, adhesion and migration into perivascular space. (Adapted from Engelhardt, 2006).

brain and also causes them to adhere on the endothelial surface more firmly.[80] At this stage lymphocyte function-associated antigen (LFA)-1 expressed on the membrane of lymphocytes, binds with intercellular adhesion molecule (ICAM)-1 or ICAM-2 expressed on the endothelial surface causing transendothelial migration of lymphocytes. The interaction between LFA-1 and ICAM-1 or ICAM-2 is considered to be crucial in the transendothelial migration of lymphocytes into the perivascular spaces of the CNS as it has been demonstrated that lack of ICAM-1 and ICAM-2 in mice fails to recruit lymphocytes into the CNS.[81] Moreover, it is important to note that lymphocyte recruitment in peripheral vascular endothelium is different than their recruitment into the perivascular area of the CNS. In the peripheral vascular endothelium, as explained above, there is a 'tethering' and 'rolling' of lymphocytes on the endothelial surface which is absent in vascular endothelium of the BBB (Fig 1B).[82] In the vascular endothelium of the BBB, there is immediate capture of the lymphocytes (predominantly T cells) followed by activation, adhesion and transmigration.[14]

Lymphocytes patrol the CNS regularly and scan for their cognate antigens in healthy as well as the inflamed

CNS .[19,22,61] It has also been demonstrated that during a strong systemic immune response, there is an increase in lymphocytes (predominantly T cells) number in the CNS.[83] Those T cells which recognise their cognate antigens/MHC complex initiate an immune reaction and reside in the CNS while those failing to recognise cognate antigens in the context of MHC molecules exit from the CNS suggesting that the entry of T cells into the CNS is dependent on their activation state rather than antigen specificity.[22,65,84-87]

The interaction between lymphocytes and cells of the CNS and antigen presentation usually occurs in the perivascular spaces of the brain known as 'Virchow-Robin' spaces.[22,63,88,89] As described previously, the initial entry of lymphocytes into the brain is suggested to be via the subarachnoid space, and/or the blood-CSF barrier, where selectins and adhesion molecules are expressed.63 Antigen presentation occurs between lymphocytes and microglial cells and also with astrocytes during neurodegenerative disease including multiple sclerosis.[90-93] Several studies have confirmed that microglial cells can express MHC-II protein and are effective antigen presenting cells.[90,91] Similarly, astrocytes also express MHC-II proteins and can act as antigen presenting cells.[92,93] Along with these cells, dendritic cells and macrophages, the professional antigen presenting cells, also help in antigen presentation to lymphocytes in the perivascular space.[90] Alternatively, it has also been shown that neurons interact with T cells via B7 ligand in the absence of MHC-II molecules as they do not express MHC-II molecules.[60]

Hence, from all these studies, it is evident that communication exists between the CNS and the immune system. These two systems are interacting via various soluble factors as well as via direct cell to cell contact. Further, it is also apparent that these two systems are not working independently or are autonomous but working together to maintain proper physiological functions. However, the precise role of immune system in healthy and diseased state of the CNS is still under investigation.

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