Neuroinflammation: Peripheral and Neurogenic Underlying Processes

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Abstract

A complex, highly specialized immunomodulatory microenvironment exists in the central nervous system, as a number of protective mechanisms against insults of different kinds have evolved over time to help in maintaining homoeostasis in this compartment.

Inflammation in the central nervous system (neuroinflammation) is an elaborate process, triggered in response to challenges of diverse nature. Characterized by increased glial activation (phagocytic phenotype) and the production of pro-inflammatory cytokines, it often leads to blood-brain barrier disruption and leukocyte invasion. While the initial response to an injury involving oxidative and nitrosative stress usually causes acute neuroinflammation, it seldom affects long-term neuronal survival. Chronic neuroinflammation, on the other side, may affect cell survival and brain functions, as observed in several neurodegenerative disorders. Various peripheral and central injuries can alter the homeostasis in the central nervous system, triggering a persistent adaptive inflammatory response that could lead to a vicious circle of neuronal damage.

The purpose of this review is to describe the most relevant players in this phenomenon, and to highlight their detrimental role in different neurologic diseases.

Keywords: Inflammation; Neuroinflammation; Neuropathologies

1. Peripherally-Triggered and Neurogenic Inflammation

Inflammation is a classical defensive response to infection and injury in peripheral tissues, and it is widely recognized as having many beneficial effects. But when this process persists for long
periods of time, detrimental effects are observed (Kerschensteiner et al., 2010). This well-known dual role of inflammation is also present in the central nervous system (CNS): therein, neuroinflammation (NI) could take part in disease resolution and even have a role in neural regeneration (Schwartz, 2010; Shechter et al., 2009), but also cause severe damage (Kerschensteiner et al., 2010).

Both systemic (peripheral) and neurogenic inflammatory processes can lead to NI. A number of systemic conditions may result in CNS inflammation and neurodegeneration (Gyoneva et al., 2014; Thomson et al., 2014). Neurogenic inflammation, on the other hand, is elicited when several molecules are released by peripheral nervous terminals or at neuronal synapses in the CNS. Peptidergic C fibers are the most important origin points to induce neurogenic inflammation, particularly at the spinal cord compartment (Xanthos and Sandkuhler, 2014).

A permanent, bidirectional, immune and endocrine communication between peripheral tissues and the CNS has been described (Besedovsky and del Rey, 2011; del Rey et al., 2008); this communication persists even in pathogenic conditions (Bottasso et al., 2013).

1.1. The Central Nervous System Is a Highly Specialized Environment

Until recent years, CNS was considered an ‘immune-privileged’ organ due to the lack of its own lymphatic system; additionally, there are no parenchymal dendritic cells (DCs) or dendritic-like cells, and the tight junctions in the cerebral vasculature limit the entry of large molecules and circulating cells in homeostatic conditions (Ransohoff and Engelhardt, 2012). Several molecules have been proposed to maintain the “immune privilege” of the CNS, including locally produced anti-inflammatory molecules such as the transforming growth factor-beta (TGF-β), melanocyte-stimulating hormone-alpha (α-MSH), vasoactive intestinal peptide (VIP), the constitutive expression of Fas ligand (FasL or CD95L), as well as complement regulatory proteins that mediate the maintenance of homeostasis in the CNS (Gimsa et al., 2013; Pegtel et al., 2014; Veerhuis et al., 2011).

Despite these peculiar immune-regulatory characteristics, CNS is continuously monitored by resident and immune cells, i.e., astrocytes, neuron microglia, and activated immune T cells (Ransohoff and Engelhardt, 2012) that trigger NI whenever injuries are detected (Gonzalez et al., 2013).

In recent years, growing evidence has been gathered pointing that the immune system, like other body systems, is under control of the nervous system; the latter can act modulating its activity, controlling the energy expenditure needed to activate it, and distributing energy requirements according to circumstantial requirements of the body (Besedovsky and del Rey, 2011; Ulrich-Lai and Herman, 2009).

1.2. Compartmentalization of the Immune Response in CNS

Anatomical components of CNS such as the parenchyma, ventricles (choroid plexus and CSF), and meninges show particular traits both in innate and adaptive immune responses. It has been
observed that the immune response to LPS in the ventricles (choroid plexus) is more rapid and intense than that in brain parenchyma (Andersson et al., 1992; Huang et al., 2008). In fact, the immune response in the ventricles, choroid plexus, meninges, and circumventricular organs is quite similar to that in the periphery. In the same way, there are marked differences with regard to the immune response in the spinal cord and brain parenchyma (Schnell et al., 1999).

1.3. Crosstalk Modulatory Activity Between Immune Cells and the Central Nervous System

CNS has immunomodulatory signals delivered to the periphery, and vice versa, peripheral signals could control the CNS. As an example, the A2A receptor for adenosine is expressed in neurons, glial cells, and in inflammatory cells (lymphocytes and granulocytes). During NI, the neuromodulator adenosine is produced. This molecule regulates microglial proliferation, chemotaxis, and immune cells reactivity through the activation of its G protein-coupled A2A receptor (Pedata et al., 2014; Santiago et al., 2014).

Recently, it has been reported that microglia may show either M1 or M2 polarization, just like peripheral macrophages (Gaikwad and Heneka, 2013). M1 phenotype may persist to sustain the inflammatory central process, while M2 phenotype has been related to anti-inflammatory response. Both phenotypes could persist during NI. In the CNS, certain phenotype M2 markers do not seem to be expressed. The best example of this is the firstly observed alternative macrophage marker, CD206, which is only seen in perivascular or choroid plexus-associated macrophages and is not expressed by parenchymal microglia (Cherry et al., 2014). In spite of this, microglial M2 has several immunomodulatory functions: it releases the anti-inflammatory cytokine IL-10 and expresses Arginase 1 (Arg1), which competes with iNOS during the effector immune response (Cherry et al., 2014). During NI, on the other side, the presence of M2 microglia attenuates the disease severity as seen in ischemic shock, Alzheimer, and spinal cord injury due to its ability to control exacerbate immune responses (Kigerl et al., 2009; Perez-de Puig et al., 2013; Yamanaka et al., 2012). It is also likely that M2 microglia may control the recruitment of peripheral cells and the activation of effector cells (Jiang et al., 2012).

Mounting evidences point to astrocytes as key players in controlling the infiltration of peripheral pro-inflammatory leukocytes into the CNS, and it has been suggested that they regulate the activity of microglia (probably via CD200 and CD200R1), oligodendrocytes, and cells of the adaptive immune system (Dentesano et al., 2014). Additionally, astrocytes are able to produce TGFβ after IL-10 stimulation (Norden et al., 2014) and to synthetize retinoic acid (RA); the latter has a protective role on blood-brain barrier (BBB) and decreases monocyte adhesion under inflammatory conditions (Mizee et al., 2014). Moreover, RA may also be involved in the induction of T regulatory (Treg) cells (Mucida et al., 2009), and thus, it is likely that astrocytes partake in maintaining a suppressive environment through RA and its effects.

Initially, it was held that BBB acted mainly as a physical barrier, limiting the passage of immune cells into CNS. However, along with this mechanical role, some cell components such as CNS pericytes may modulate the entry of immune cells into the brain. Pericytes, often regarded as “brain macrophages”, make up the interface between the immune system and CNS by secreting chemo-attractant molecules and inflammatory mediators such as IL-1β, IL-6, tumor necrosis factor.
alpha (TNF-α), reactive oxygen species, nitric oxide (NO), and matrix metalloproteinases (MMP-2 and MMP-9) (Kovac et al., 2011). Also, pericytes derived from human pluripotent stem cells are able to modulate Treg induction (Domev et al., 2014).

Although neurons are not considered as immune cells, they share with them receptors for neuropeptides which act as pro-inflammatory and anti-inflammatory molecules. The two closely related neuro-protective peptides, vasoactive intestinal peptide (VIP) and pituitary adenylyl cyclase-activating peptide (PACAP), are known to protect neurons and also show other physiological functions (Malva et al., 2012). These neuropeptides are not only implicated in regulation of sympathetic neurotransmission and cell survival in postganglionic sympathetic neurons (Drahushuk et al., 2002; Tompkins et al., 2010), but are also able to inhibit the production of macrophages and microglia, the release of inflammatory mediators such as TNF-α and IFN-γ, and the polarization of T cell responses away from Th1/Th17 and towards a Th2 phenotype. More recent studies have revealed that these peptides can also promote the production of both natural and inducible subsets of peripheral regulatory T cells (Waschek, 2013).

Additionally, several neuron-expressed molecules (CD22, CD47, CD200, NCAM, semaphorines, and CD56) have been proved to promote immune-modulatory actions on microglia and glial cells (Tian et al., 2009). Neurons are also capable of interacting with the immune system by producing chemokines (fractalkine/CX3CL1) (Limagola and Ransohoff, 2014), growth factors (NGF) (Aloe et al., 1994), and neuropeptides (substance P and neuropeptide Y) (Buttari et al., 2014; Jiang et al., 2012). It has also been described that substance P mediates immunomodulatory effects on immune cells (Jiang et al., 2012).

Finally, the crosstalk between neurons and the immune system involve neurotransmitters and their receptors (dopamine, glutamate, acetylcholine, and GABA, among others) (Al-Amin and Reza, 2014). Their effects depend on the type of receptor being expressed in immune cells, the expression level, and the surrounding microenvironment.

2. Regulating Neuroimmune Inflammation

2.1. The Neuro-Immune-Endocrine Circuitry

In certain circumstances, the complex interactions in the neuro-immune-endocrine circuitry may lead to down-regulation of both innate and adaptive immunity. CNS is able of sensing the internal status and the outside environment through the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-gonadal (HPG) axis, and the neuroimmune system.

2.1.1. The Neuroimmune System

CNS is relatively sheltered from the peripheral immune system; in fact, it has a local immune network where glial cells have both immune and metabolic roles. The modulation of these processes requires the combined participation of the autonomic (sympathetic and parasympathetic branches) and the immune system.
The sympathetic nervous system (SNS) innervates the adrenal gland, resulting in the secretion of catecholamines (CA) into the systemic circulation; in turn, CA up-regulate the transcription of pro-inflammatory cytokines (Nance and Sanders, 2007). CA can modulate the proliferation and differentiation of immune cells, as well as cytokine production (Flierl et al., 2008; Peng et al., 2004; Torres et al., 2005). In this context, the sympathetic nervous system is also able to modulate the induction of Treg cells (Bhowmick et al., 2009) via a TGF-β-dependent mechanism, thus acting as a bridge between the immune and the nervous systems.

Additionally, immune cells do not only express CA receptors but also produce CA in an autocrine way (Flierl et al., 2007; Marino et al., 1999). CA seem to selectively affect Th1 helper lymphocytes; this is related with the expression of the β2 adrenoreceptor (β2 AR) (Sanders et al., 1997). In this sense, CA can exert inhibitory effects not only on Th1 but also on NK lymphocytes (Dokur et al., 2004).

The parasympathetic nervous system (PNS), on the other side, modulates the immune response through the vagus nerve. The afferent component of this nerve can signal the presence of peripheral inflammation to the brain through IL-1 receptors expressed in parasympathetic ganglia.

The immunomodulatory properties of the vagus nerve were initially characterized with regard to the inflammatory response in sepsis. A neuroimmune feedback mechanism called cholinergic reflex modulates the vagal activity. Acetylcholine (Ach) acts through two types of receptors: muscarinic and nicotinic; macrophages express the α7 subunit of the nicotinic receptor, while lymphocytes express both receptor types. Activated macrophages can diminish the production of pro-inflammatory cytokines like IL-1β, IL-6, and IL-18 through a post-transcriptional mechanism (Borovikova et al., 2000). The cholinergic anti-inflammatory pathway is associated with efferent activity in the vagus nerve, leading to Ach release in the reticuloendothelial system and inhibiting the production of TNF-α by macrophages (Thayer, 2009). The latter mechanism, however, has been questioned. Experimental evidences have supported the participation of a distinct sympathetic anti-inflammatory pathway mediated by adrenergic receptors (Rosas-Ballina et al., 2011).

The vagus nerve also connects with the spleen via the splenic nerve, which releases noradrenaline. In an ex vivo model of endotoxemia, it was demonstrated that noradrenaline-treated splenic lymphocytes release Ach. T cells (also releasing Ach) were able to relay the inflammatory response of macrophages (Rosas-Ballina et al., 2011).

2.1.2. The Endocrine System

The hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-gonadal (HPG) axes critically participate in the regulation of NI. In response to stress, several cytokines are expressed in the hypothalamus: IL-1β, IL-6, and TGF-β (Hueston and Deak, 2014). Corticotrophin-releasing factor plays a central role in regulating stress response; this hormone is released by hypothalamic neurons, which can respond to both cytokines and autonomic inputs (Kageyama et al., 2010; Serrats and Sawchenko, 2006).
HPA activation results in the production of glucocorticoids (GCs). These important hormones act on several immune cell types. Particularly, cortisol has strong immunomodulatory effects on T cell activation, the expression of adhesion molecules, cell migration, and cytokine production (Bellavance and Rivest, 2014). On the other side, the HPG axis exerts immune modulation through gonadal steroids, particularly 17-β estradiol (E2) and progesterone, known also as neuroactive steroids given their influence on neurons, astrogia, microglia, and oligodendrocytes. E2 can modulate the immune response of microglia during acute brain injury. It reduces the expression of several immune signaling such as TNF-α, monocyte chemoattractant protein-1 and macrophage inflammatory protein-2 (Giatti et al., 2012; Johann and Beyer, 2013; Vegeto et al., 2008). Gonadal steroids also participate in immune regulation; indeed, estradiol enhances the functions of Treg cells (Valor et al., 2011). In vitro experiments show that estrogen may have a direct impact on B and T cells by inducing rapid signaling events such as Erk and AKT phosphorylation, cell-specific Ca(2+) signal, and NF κB activation mediated by classical estrogen receptors (Adori et al., 2010). Progesterone is also a nuclear immune regulatory hormone that induces a potent Treg activity, associated with the suppression of the immune response by promoting mTOR pathway (Lee et al., 2012).

3. Pathologies and Neuroinflammation

Neuroglial cells are particularly susceptible to the harmful effects of oxidative stress. Microglia and astrocytes release inflammatory mediators in response to oxidative stress (Cahill-Smith and Li, 2014; Chiurchiu and Maccarrone, 2011; Fuller et al., 2010). Reactive oxygen species (ROS) can activate inflammatory responses in the CNS by stimulating redox-sensitive transcription factors, including the nuclear factor κB and activator protein-1 (AP-1) (Chiurchiu and Maccarrone, 2011). These factors increase the synthesis of inflammatory mediators such as 5-lipoxygenase (5LOX); the nitric oxide synthase (NOS) isoforms; cytokines (particularly TNF-α); chemokines; immunoglobulin Fc receptors (FcγR); adhesion molecules like P- and E-selectine, VCAM-1, and ICAM-1 (Sandireddy et al., 2014), as well as matrix metalloproteinases (MMPs), cytosolic phospholipase A2 (cPLA2), and cyclooxygenase-2 (COX-2) (Hsieh and Yang, 2013); all of them promote an inflammatory environment. The O2⁻ radical can interact with NO to produce ONOO⁻; this molecule is highly oxidant by itself, and it can also be cleaved into OH⁻ and NO₂, both of them strong oxidants (Zalba et al., 2001). Oxidative stress has been linked to the pathogenesis of Alzheimer disease (Shi and Gibson, 2007), Parkinson disease (Halliwell, 2006), and cerebrovascular disorders (Olmez and Ozyurt, 2012).

3.1. CNS Disorders

3.1.1. Alzheimer Disease

Alzheimer disease (AD) is the most common type of dementia, usually affecting people over 65 years of age. β-amyloid (Aβ) plaques are associated with microglial and astrocyte activation, along with increased humoral inflammatory factors in AD (Hensley, 2010; Mosher and Wyss-Coray, 2014).
Clumps of activated microglia appear on senile plaques, and many similar accumulations are evident in the surrounding tissue. Generalized astrogliosis manifested by cell hypertrophy and an increase in the expression of glial fibrillary acidic protein (GFAP) can also be found (Verkhratsky et al., 2010). A direct relationship between astrocyte change and the increase of senile plaques has been reported (Simpson et al., 2010).

With respect to humoral factors, serum and CSF inflammatory markers have been found increased in several studies (Britschgi and Wyss-Coray, 2009; Lee et al., 2009a; Lee et al., 2009b; Olson and Humpel, 2010). The cytokines and chemokines most frequently found associated to AD were IL-1(α and β), IL-4, IL-6, IL-10, TGF-β, and MCP-1 (Lee et al., 2009b). Longitudinal studies assessing the possible correlation between AD incidence or the worsening of patients’ cognitive status and inflammatory markers have been performed, with discordant results. Low C-reactive protein levels were found associated with a more rapid cognitive decline in patients with a diagnosis of probable AD (Locascio et al., 2008), while high levels of α1-antichymotrypsin, IL-6, and C-reactive protein were associated with an increased risk of AD in another study (Engelhart et al., 2004). Particularly, IL-1β seems to be a main factor in the progression of the disease (Tan et al., 2007).

It is already evident the existence of a communication between the peripheral and the central inflammatory status. In AD, in addition to the increase of some cytokines in the periphery, changes in the phenotype of peripheral cell subpopulations were found. In particular, a decrease in the number of B lymphocytes with respect to control subjects of similar age and sex has been reported, linked to an increase of activated CD8 cells expressing CD71 and CD28 (Pellicano et al., 2010; Speciale et al., 2007). After activation with recombinant β-amyloid peptide, an increase in the expression of activation marker CD69 was observed, but no changes were found in CD25 (Pellicano et al., 2010).

Treg cells are critical in controlling inflammation since they down-regulate pro-inflammatory cytokines and ROS, and also induce apoptosis of effector cells. In an experimental AD model, Tregs previously stimulated with Aβ protein increased the removal of amyloid plaques (Fisher et al., 2010). A study found an increase in Tregs with phenotype CD4+CD25highFoxp3+ and phenotype PD1+ (programmed death receptor 1) in AD patients, some with mild cognitive disorders, when compared to controls. Interestingly, the Treg subpopulation with higher suppressive capacity (TregPD1) was especially high among patients with mild cognitive disorders (Saresella et al., 2010). These results reinforce the postulated importance of controlling inflammation in AD pathogeny, as well as the protective role of Tregs (Saresella et al., 2010).

3.1.2. Parkinson Disease

Parkinson disease (PD) is the second most common progressive neurodegenerative disorder, only after AD, with a prevalence of 0.5-1% among people older than 65 years. A protein aggregation of α-sinuclein has been described, leading to Lewy bodies and Lewy neuritis with extensive gliosis, particularly in substantia nigra (Hirsch and Hunot, 2009).
Activated microglia and astrocytes have been found in postmortem brain examination of PD patients. Infiltrating cytotoxic CD4+ and CD8+ T cells in the substantia nigra of PD patients have been observed in a postmortem study (Ferrari and Tarelli, 2011).

Increased levels of cytokines (including IL-1β, TGF-β, IFN-γ, and IL-6) were measured postmortem in the CSF and nigrostriatal regions from individuals with PD with respect to age-matching healthy controls (Blum-Degen et al., 1995; Mount et al., 2007).

*In vivo* evidences of increased BBB permeability have been given by PET measurement of ligand uptake by the molecular efflux pump, P glycoprotein, and increased albumin levels in CSF from PD patients (Kortekaas et al., 2005; Pisani et al., 2012). Increased BBB permeability could allow for an augmented influx of peripheral adaptive immune cells, which then would be activated by inflamed microglia. This inflammatory response could induce neuronal injury, which in turn would propagate a positive-feedback cycle of neuronal injury and inflammation in the development of PD (Tansey and Goldberg, 2010).

Increased levels of the systemic cytokines TNF-α, IL-2, IL-6, and RANTES (Collins et al., 2012) have been detected in serum from PD patients. In one study, high plasma IL-6 levels correlated with increased risk to develop PD (Chen et al., 2008). Also, serum IL-6 levels correlated with clinical severity (Koziorowski et al., 2012). A peripheral decrease in the number of CD4+ cells and an increase in CD4bright+CD8dull+ cells were also reported (Hisanaga et al., 2001). A recent study showed that an increase in the effector/memory T cells correlate with the severity of motor disability in PD patients. Also, impaired abilities of regulatory T cells to suppress effector T cell function were observed in PD patients when T cell phenotype and function were compared with matched controls. These data support the concept that chronic immune stimulation is linked to PD pathobiology and severity (Saunders et al., 2012).

In a PD murine experimental model, Tregs showed neuroprotective activity. This fact is probably related to a suppression of the active microglial response (lowering the production of inflammatory cytokines and ROS) and to an overregulation of molecules such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), cytokine IL-10, and TGF-β (Reynolds et al., 2007; Reynolds et al., 2010). Altogether, these findings suggest that Tregs could have a protective activity in PD by controlling NI and also by modulating the microglial response, defining the balance between damage and protection. It was proposed that IL-4 production by Tregs could favor a microglial M2 protective phenotype (Beers et al., 2011).

### 3.1.3. Epilepsy

The first evidences about the link among immunity, inflammation, and epilepsy arose from the antiepileptic properties of ACTH and corticosteroids in various pediatric cases (Wheless et al., 2007). The worsening of most epileptic seizures with concurring infections and the existence of febrile seizures also suggested the role of an immuno-inflammatory condition in the occurrence of epilepsy (Dube et al., 2007).
Several clinical studies demonstrated an increase in the levels of inflammatory mediators (IL-6, TNF-α, IL-1β, and its receptor IL1R1) in serum and CSF from epileptic patients (Aronica and Crino, 2011).

More recently, histological studies on brain tissue surgically removed from patients suffering epilepsy unrelated to inflammation showed the induction of several inflammatory signaling pathways, the overexpression of genes coding for pro-inflammatory chemokines and cytokines, and a prominent activation of microglia and astrocytes (Boer et al., 2010; Choi et al., 2009; Iyer et al., 2010a; Iyer et al., 2010b; Ravizza et al., 2008). The presence of peripheral immune cells in the brain tissue, and more recently the activation of the toll-like receptors (TLR) signaling pathway, have been demonstrated (Pernhorst et al., 2013; Zattoni et al., 2011). Studies using positron emission tomography (PET) with the C-PK11195 tracer (specific for activated microglia) confirmed these findings in patients with epilepsy secondary to encephalitis (Banati, 2002; Kumar et al., 2008) or with focal cortical dysplasia (Butler et al., 2013). These findings confirmed that the immune-inflammatory phenomenon is intrinsically linked to epilepsy, regardless of its etiology.

The use of experimental models allowed a deeper exploration of the causal relationship between epilepsy and inflammation. These models showed that recurrent seizure crises induce NI, with activation of microglia, astrocytes, neurons, and BBB epithelial cells (Vezzani and Ruegg, 2011). It was also demonstrated that systemic inflammation and NI favor crisis occurrence and worsen the pathology. It was found in particular that pro-inflammatory cytokines released by glia have a significant role in the neuronal hyperexcitability involved in the onset of epileptic crises and in its recurrence, and also in the ensuing excitotoxic cell damage (Devinsky et al., 2013). On the other hand, pharmacologic blocking or inactivation of various pro-inflammatory pathways (IL-1, α and β), TNF-α, COX-2) or some elements from the signaling pathway TLR yielded potent anticonvulsant effects (Maroso et al., 2011a; Maroso et al., 2011b; Ravizza et al., 2008). Additionally, mice overexpressing the soluble form of human IL-ra in astrocytes, as well as mice lacking the ICE/Caspase-1 gene or IL-1R gene, both of which are unable to produce and release IL-1β or to activate IL-1β signaling, show a significant delay in the onset of epileptic crises and are intrinsically resistant to epileptogenic activity (Maroso et al., 2011b; Vezzani et al., 2000).

3.1.4. Spinal Cord Injury

Spinal cord injury (SCI) induces chronic pain due to an extensive local inflammatory reaction (i.e., NI). It is accompanied by increased macrophage, microglia, and astrocyte activation, with accumulation of neutrophils, T, and B cells when compared to traumatic brain injury (Batchelor et al., 2008; Zhang and Gensel, 2014). In this context, studies in an animal model showed that SCI is able to induce inflammatory changes in hypothalamus, hippocampus, and the cerebral cortex. Some impairment of the cognitive function was also observed in tested animals (Wu et al., 2014). Additionally, it was observed in a mice model that external infiltration of macrophages in SCI favored tissue recovery (Shechter et al., 2009); similar findings have been reported on non-mammalian vertebrate species (Kyritsis et al., 2014).

While autoimmune T cells promote NI, they were found to participate in the repairing process in an animal SCI model (Hauben et al., 2000). An interesting data to point out is that some cytokines

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(like TNF-α) can be transported in an anterograde way from peripheral tissues to the spinal cord (Shubayev and Myers, 2001), leading to the activation of glial cells. Neuronal activation may also reinforce the inflammatory response through a neurogenic mechanism.

3.2. Peripheral Diseases: Obesity and Hypertension

Metabolic syndrome, a condition widely spread in the world (Hotamisligil, 2006), is characterized by several related chronic pathologies such as visceral obesity, insulin resistance, hypertension, and hyperlipidemia (Gallagher and LeRoith, 2010). Obesity, the main driver of those metabolic disorders, is accompanied by persistent, low-grade inflammation that negatively impacts on target peripheral tissues such as adipose tissue and vascular endothelium, resulting in the development of type-2 diabetes and cardiovascular diseases (Panza et al., 2010). Epidemiological, clinical, and experimental approaches have revealed that obesity induces NI (Beydoun et al., 2008; Lee et al., 2009a), not only by impacting on peripheral functions that CNS controls, but also by activating microglia and astrocytes, two of the CNS cellular types critically involved in NI.

Obesity, a condition where body mass index (BMI) is higher than 30, is caused by excessive caloric intake and storage (overnutrition) along with scarce physical activity. Hypertension (high peripheral blood pressure) may have several etiologies (from genetic to obesity-associated); the damage to the vascular endothelium by continuous chronic inflammation during obesity plays a critical role in the disease (Rahmouni et al., 2005). Both physiological alterations induce low-grade inflammation, characterized by higher levels of activated innate and adaptive immune cells (dendritic cells, macrophages, and NK cells), as well as pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, and IL-18 produced by adipose tissue, the affected vascular endothelium, and the activated immune cells (Monteiro and Azevedo, 2010; Rodriguez-Iturbe et al., 2014). A wealth of experimental evidence has linked the IKKβ/NF-κB pathway with the production of inflammatory cytokines through TLR and TNFα receptors (Purkayastha et al., 2011; Romanatto et al., 2009). The peripheral low-grade inflammatory response in these pathological conditions results in hypothalamic inflammation (characterized by reactive gliosis, involving both microglial and astroglial cell populations). In turn, this increases the appetite and caloric intake by up-regulating the body weight homeostasis in the paraventricular nucleus of the hypothalamus, affecting also cardiovascular functions and blood pressure (de Kloet et al., 2014; Rui, 2013). Altogether, these settings promote neuron injury, resulting in the alteration of cognitive functions (Elias et al., 2003) and may favor neurodegenerative diseases like AD and PD (Bousquet et al., 2012; De Felice and Ferreira, 2014).

How brain inflammation is initiated during both obesity and hypertension is a debatable issue, under continuous investigation. Experimental studies in animal models support the participation of peripheral circulating cytokines and of adiponectin, free fatty acids, and the hormone leptin in activating brain immune cells (Cani et al., 2008; Duparc et al., 2011; Milanski et al., 2009; Wisse et al., 2004) and in brain atrophy (Rajagopalan et al., 2013). Indeed, certain long-chain saturated fatty acids have been shown to penetrate brain regions through the circumventricular organs, which lack of an effective BBB: these fatty acids activate microglia and astrocytes, mainly through the TLR-4 signaling pathway, initiating the inflammatory cascade (Milanski et al., 2009) that results in the local expression of pro-inflammatory cytokines and endoplasmic reticulum stress. Peripheral
inflammatory cytokines, chemokines, and activated immune cells can also promote NI, by stimulating centrally efferent neurons and increasing BBB permeability, thus allowing peripheral cytokines and the immune cells themselves to enter the brain (Lu et al., 2009).

On the other side, angiotensin II, the pivotal vasoactive hormone of the renin-angiotensin system in the cardiovascular homeostasis, may be involved in microglial activation (Shi et al., 2010) during hypertension. In addition, as it was the case with obesity, peripheral pro-inflammatory cytokines and activated immune cells may promote and sustain hypertensive conditions, and have a role in the microglial activation and astrogliosis that accompany the inflammatory response observed during the development of neurodegenerative diseases (Rodriguez-Iturbe et al., 2014).

4. Conclusions

The central nervous system constitutes a highly specialized compartment, with specific responses against harmful events and alterations of homeostasis. The old concept of an “immune privileged organ” and the notion of blood-brain barrier as a mechanical limit gave place to a more refined view, accounting for the complex communication between the central nervous system and the periphery.

The dual role of inflammation, recognized as a beneficial response to injury but also as an agent that triggers or exacerbates tissue damage, is present in the nervous central system as well. Acute neuroinflammation may help to restore homeostasis and even promote neural regeneration, but chronic neuroinflammation is known to induce the formation of oxygen and nitrogen reactive species, both of which result in neurodegeneration.

Neuroinflammation has been found associated to neurogenic lesions, or triggered by events in the periphery. Examples of disorders linked to neurogenic inflammation are Parkinson disease, Alzheimer disease, epilepsy, and spinal cord injury. Obesity and metabolic syndrome, on the other side, are systemic conditions capable of inducing neuroinflammation and neuronal damage.

A deeper understanding on the underlying mechanisms of neurogenic and peripherally-triggered neuroinflammation will provide us with knowledge and tools to modify its outcome, which would eventually allow us to treat neurodegenerative diseases and to prevent the neuronal degeneration caused by obesity and other metabolic disorders.

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