Antioxidants and Redox Signaling

DOI: 10.1089/ars.2020.8076

FORUM REVIEW ARTICLE

Inflammation in neurological disorders: the thin boundary between brain and periphery

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Word numbers: 8830

References numbers: 219

Illustration (grey-scale) numbers: 5

Keywords: Alzheimer's disease; inflammation; multiple sclerosis; vascular dementia

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This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

ABSTRACT

Significance: Accumulating evidence suggests that inflammation is a major contributor in the pathogenesis of several highly prevalent, but also rare, neurological diseases. In particular, the neurodegenerative processes of Alzheimer disease (AD), vascular dementia (VAD), Parkinson's disease (PD), multiple sclerosis (MS) are fueled by neuroinflammation, which in turn is accompanied by a parallel systemic immune dysregulation. This cross-talk between periphery and the brain becomes substantial when the blood brain barrier loses its integrity as often occurs in the course of these diseases. It has been hypothesized the perpetual bidirectional flux of inflammatory mediators is not a mere "static" collateral effect of the neurodegeneration, but represents a proactive phenomenon sparking and driving the neuropathological processes. However, the upstream/downstream relationship between inflammatory events and neurological pathology is still unclear.

Recent Advances: Solid recent evidence clearly suggest that metabolic factors, systemic infections, Microbiota dysbiosis, and oxidative stress are implicated, although at different extent, in the development in brain diseases

Critical Issues: Here, we reviewed the most solid published evidence supporting the implication of the axis systemic inflammation-neuroinflammation-neurodegeneration in the pathogenesis of AD, VAD, PD and MS, highlighting the possible cause of the putative downstream component of the axis.

Future Directions: Reaching a definitive clinical/epidemiological appreciation of the etiopathogenic significance of the connection between peripheral and brain inflammation in neurologic disorders is pivotal since it could open novel therapeutic avenues for these diseases.

1. Introduction

Inflammation can be defined as an attempt of innate and adaptive immune cells to eliminate the initial cause of a cell injury (219). These defensive actions firstly consist in the release of cytokines, chemokines and other chemical mediators that modulate the complex immune response. This response occurs via activation of transcription factors such as nuclear factor κ B (NF-κB), activator protein-1 (AP-1), nuclear factor of activated T cells (NFAT), and signal transducer and activator of transcription-3 (STAT3) (105, 138, 173). Cellular insults can also activate cytosolic multiprotein complexes called inflammasomes, which regulate host immune response against pathogen infections and cellular stress (105). Although inflammation is a protective response, chronic inflammation contribute to tissue injury and disease onset/progression.

Neuroinflammation is primary driven by microglia, the resident macrophages in the brain, and astrocytes, cells that in non-pathological conditions play central role in many aspects of brain metabolism and physiology having a key-role in maintaining blood brain barrier (BBB) integrity (163). If acute neuroinflammation plays a protective role in the body, chronic neuroinflammation is always harmful to the central nervous system (CNS) (70). Increasing evidence suggests that the pathogenesis of neurological diseases such as Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease (PD) and multiple sclerosis (MS) is not restricted to the neuronal compartment, but includes strong interactions with immunological mechanisms in the brain. One of the common feature of these diverse diseases is that their neuropathological hallmarks differently interact with microglia and astroglia, and trigger an innate immune response characterized by the release of inflammatory mediators, contributing to the disease progression and severity. However, the precise role of neuroinflammation in the etiology and pathomechanisms of the aforementioned neurological diseases is still controversial, ranging from representing a possible cause to being a by-product of the disease or even being beneficial (62, 184, 194, 196).

Brain is separated from the rest of the body by BBB to form a classically described immune-privileged organ. Actually, the concept of immune isolation of the brain has been questioned in the last decades. Indeed, it is true that CNS shows attenuated responses to challenge by alloantigen, but it is also true that it shows local inflammation in response to

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infection (55). Moreover, abundant evidence suggests that communication between systemic and CNS immune system is possible through cytokines mining the integrity of BBB, thus allowing the cross-passage of these mediators and permitting leukocyte migration into the brain (114, 181). These blood-borne immune cells are documented to be highly neurotoxic and represent an additional critical component in mediating neuroinflammation (163). The cross-talk between periphery and brain occurs also in the absence of a non-physiological leakage of BBB by many alternative routes. The results of this continuous connection between two somehow independent worlds, make them reciprocally vulnerable to perturbations of metabolic, but also immune, homeostasis occurring in one world. According with this reasoning, there is a wealth of evidence showing how systemic inflammation, caused by infections, metabolic disease, environmental stressors, oxidative stress (OxS) etc. could lead to microglia and astroglia activation, and eventually trigger, and/or contribute to, neurodegenerative processes.

2. Neuroinflammation

The term “neuroinflammation” encompasses the inflammatory processes occurring in the CNS involving both the innate and adaptive immune system (27). The main cell players in neuroinflammation are different from those involved in other organ/tissue. Indeed, brain is believed to be an “isolated system” that is challengingly reached by cells, including immune cells, at least in the absence of inflammation or injury. Neuroinflammation involves a coordinated response between microglia and other CNS cells, such as astrocytes, with the latter cells receiving and amplifying inflammatory signals from the former (114). Microglia are the resident immune cells of the CNS, which normally respond to neuronal damage and remove the damaged cells by phagocytosis (186). Healthy brain’s microglia are defined as resting, although, paradoxically, their processes are perpetually elongating and retracting to explore the neuronal environment. Through this ability to probe the surrounding brain parenchyma, microglia contributes to preserving plasticity of the neuronal circuits, and to protecting and remodeling synapses (95). In vivo studies have demonstrated that in aging CNS microglia have an exaggerated propensity to respond to inflammatory stimuli, similar to that observed in brains with ongoing degeneration (141). This so-called “priming” process appears to be driven by aging of microglia, or by changes in their microenvironment, due to, among others, infiltration of peripheral cytokines (141).

This state of chronic activation makes these cells susceptible to a secondary inflammatory stimulus, which can then trigger an uncontrolled inflammatory response (70).

Activation of microglia appears to be heterogeneous with two alternative functional phenotypes: the M1 (pro-inflammatory) phenotype and the M2 (anti-inflammatory) phenotype (183). These different activation statuses of microglia are characterized by secretion of different arrays of cytokines. M1 microglia originally respond to the injury and infection, acting in the first line to defense tissue, but they also can yield neurotoxic effects.

Astrocytes are the most abundant cells in the brain and, alike microglia, regulate multiple aspects of neural tissue homeostasis (74). Astrocytes are important structural and functional components of the BBB; through their end-foot processes that unsheathe 99% of the surface of brain microvessels, astrocytes regulates diffusion of solutes and water between blood vessels and brain parenchyma (101). Astrocytes become reactive in response to injury and inflammation (93) the so-called astrogliosis is a defensive response to pathological conditions that affect the CNS (trauma, ischemic damage, neuroinflammation, or neurodegeneration). This disease-specific process develops as hypertrophy and proliferation of astrocytes associated with upregulation of glial fibrillary acidic protein (GFAP), an astrocytes hallmark. GFAP is the main component of astrocytes intermediate filaments (IFs) that are primarily involved in signaling among brain cells, and controls their stress responses, both in health and disease (140).

3. Neuroinflammation in Alzheimer's disease, vascular dementia, Parkinson's disease and multiple sclerosis

A. Alzheimer's disease: pathogenesis and main pathophysiological traits

Dementia affects over 40 million people worldwide, and is one of the major causes of disability and death among elderly people (150). Sporadic Alzheimer's disease is the most common form of dementia in elderly populations with nearly 70% of patients. Dementia is often preceded by a mild symptomatic phase (mild cognitive impairment: MCI) (144), characterized by short-term or long-term memory impairment which is not associated with functional disability; 8-15% of MCI converts to dementia annually.

The neuro-pathological hallmarks of AD include the deposit extracellular amyloid-β (Aβ) peptide (Aβ1-40 and Aβ1-42) accumulated in extracellular senile plaques and intracellular

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neurofibrillary tangles (NFT) primarily consisting in abnormal and hyper-phosphorylated Tau protein (36). The deposition of amyloid plaques and NFTs is estimated to start more than a decade before the earliest symptoms of cognitive decline. Of note, the progress of this pathology is characterized by brain atrophy, reflecting neuronal shrinkage and death and synaptic and axonal loss (38).

The most hold hypothesis on AD poses the amylodogenic process as primary cause (amyloid cascade hypothesis) (66). Aβ derives from a large type I transmembrane protein, the amyloid precursor protein (APP) which is cleaved sequentially by proteases, β- and γ-secretase (35). A third enzyme, the α-secretase, catalyzes the nonamyloidogenic proteolysis of APP (156).

However, the precise role of Aβ in AD pathology and whether most AD represents a primary or secondary amyloidosis remains an open question. This lack of certainty gives rise to a number of other hypotheses pointing to other “aberration” as primary trigger for the disease development. The most accredited alternative candidate is the other core pathology, NFT due to Tau hyper-phosphorylation which leads to loss of neuronal function, and ultimately apoptosis (156). Other hypotheses that are worth it to mention, are those related to mitochondrial dysfunction, energy crisis and cerebrovascular damage as triggering events of the disease (38, 156).

The general picture that has emerged after several years of extensive and productive research investigating the mechanisms responsible for AD is that none of the aforementioned proposed pathogenic models can fully capture what really occurs from the onset to the last stage of the disease. One of the possible solution for unravelling this complex scenario could be to find that “string” that connects the well-established AD neuropathological hallmarks (95).

A.1. Neuroinflammation in Alzheimer’s disease

In the last decade, the view of the role of neuroinflammation in AD pathogenesis has changed: from a simple response to the well-established neuropathological hallmarks, to a major contributor in the progression of the disease. Indeed, in brain of AD patients was found a sustained inflammation, in proximity to Aβ plaques and NFT (153). Subsequently, large clinical- epidemiological studies demonstrates that anti-inflammatory treatments showed protection against AD development, with near to 50% risk disease decrease in

patients who are long-term nonsteroidal anti-inflammatory drug (NSAID) users (16, 21). However, although confirmed in AD animal models, the use of NSAIDS in AD treatment did not find a definitive corroboration in human trials (123).

In AD, the activation of microglia is the result of the presence of Aβ; the aberrant deposit of protein can be detected by several sensors, including toll-like receptors (TLRs), Triggering receptor expressed on myeloid cells 2 (TREM2), receptor for advanced glycation end products (RAGE) and cytokines and chemokines receptors (214). Aβ can promote the NF-κB and mitogen-activated protein kinase (MAPK) pathways, triggering release of pro-inflammatory cytokines and ROS/RNS that can contribute to neurotoxicity.

A sustained inflammation leads to compromised clearance of Aβ and their accumulation in the brain (95). This effect is mainly caused by the fact that in a chronic inflammation state, microglia progressively lose the ability to eliminate Aβ but maintain unaltered the overproduction of pro-inflammatory cytokines exacerbating the neuroinflammation thus increasing Aβ accumulation. As it will be illustrated later on, cerebral infiltration by peripheral macrophages may also contribute to further worsen the effects of sustained inflammation.

As anticipated, Aβ fuels a self-perpetuated vicious cycle by pro-inflammatory cytokines release.

tumor necrosis factor- α (TNF-α) is the main pro-inflammatory molecule involved in AD (45) and it is over expressed in activated microglia, reactive astrocytes and other cell types upon brain damage/disease (155). In vitro studies showed that Aβ is able to up-regulate TNF-α expression that in turns can stimulate the expression of APP and β- and γ-secretase activity, leading to increase Aβ burden peptides in large amounts (18, 45).

Interleukin (IL)-1β is also a master regulator of neuroinflammation. It is produced by microglia, astrocytes endothelial cells, neurons and oligodendrocytes ad acts as a downstream regulator of a vast array of cytokines, including TNF-α and IL-6, and chemokines, prostaglandins, ROS, RNS etc.. High levels of IL-1β were detected in microglial cells surrounding Aβ plaques in AD patient brains and cerebrospinal fluid (CSF). In vitro studies showed that IL-1β is released by activated microglia in response to Aβ exposure (71). IL-1β itself may promote Aβ deposition and aggregation by upregulating APP mRNA and or enhancing its proteolysis (154).

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Notably, an increase of anti-inflammatory cytokines exhibits AD neuro-protective proprieties (37, 95, 115, 164).

B. Vascular dementia: pathogenesis and main pathophysiological traits

Vascular disease (VAD), which is an orphan disease, is caused by cerebrovascular disease being the second most common form of dementia (about 20% of cases) (61). The most frequent VAD subtypes are multi- and single infarct dementia, small vessel disease and AD-VAD mixed dementia (simultaneous presence of stroke induced-white matter lesion and amyloid plaques). Cognitive impairment in VAD patients is mostly attributable to inter-correlated conditions such as hypoperfusion, ischemic and hemorrhagic hypoxia caused by stroke, leading to the characteristic white and grey matter lesions (135). Indeed, brain functionality needs a continuous blood supply (217). Notoriously, cerebrovascular disease is now recognized not only as a primary cause of cognitive impairment, but also as pathogenic co-factor and/or coexisting condition of other forms of dementia, including AD (174).

Hypoperfusion is often consequence of microangiopathy (i.e. cerebral small vessel disease) or macroangiopathy (e.g. atherosclerosis), which in turn are caused by common cardiometabolic risk factors (e.g. hypertension, smoking, diabetes, etc.) and neurovascular aberration specifically related to AD (i.e. cerebral amyloid angiopathy) (174). Decrease in cerebral blood flow, that is often observed prior to the onset of dementia (81), can accelerate neurodegeneration, BBB disruption, and neuroinflammation (201, 216).

White matter is highly vulnerable to vascular insufficiency; dysregulation of cerebral blood flow has been mostly attributed to dysfunction of cerebrovascular endothelial cells (CerEC), but also other components such as glia, neurons, vascular cells, and matrix component (62). Endothelial dysfunction also leads to loss of integrity of BBB, an early event of VAD pathogenesis (81). Indeed, CerECs are the main structural components of BBB (other components are: astrocytes, pericytes, neurons, and basement membrane) that ensures proper CNS functions (142).

Chronic and acute hypoxia/hypoperfusion bring about excitotoxicity, activation of CerECs and OxS, all events that concur to brain lesions (36, 102). In particular, elevated levels of ROS reduce nitric oxide (NO) availability thus, affecting endothelial relaxation (201). This

phenomenon along with intraluminal shear stress leads to endothelial activation, expression of chemoattractant molecules and inflammatory response (48).

B.1. Neuroinflammation in Vascular dementia

The implication of inflammation in VAD, is demonstrated by high levels of several pro-inflammatory cytokines (IL-1β, TNFα), and reactive microglia and astrocytes in the damaged white matter (7, 167). After the stroke (major cause of VAD), there is a rapid and massive release of pro-inflammatory signals from activated microglia and astrocytes, that lead to the infiltration of immune cells into the ischemic region exacerbating brain damage (85).

The activation of microglia is rapid, and animal models showed that the severity of injury may be reflected in the state of microglial activation which could be related to the expression of CD14 receptors followed by TLR-4 (215).

Microglia-mediated neurotoxicity depends on production of ROS, cytokines, and MMPs-2/-3/-9 that actively participate to the disruption of BBB (201, 208). In turn, this dramatic event leads to the entry of inflammatory cytokines and cells from the periphery, that sustain microglial activation, giving rise to a detrimental self-enhancing cycle (192, 201).

Following hypoxia/hypoperfusion, numerous signaling molecules, such as transforming growth factors-α, IL-6, ciliary neurotrophic factor etc., released from neurons, microglia, and dysfunctional CerECs cause astrocytes activation (139). These cells become hypertrophic increasing expression of inflammatory factors like MCP-1, IL-1β and GFAP. The main defensive response of astroglia is to restrict the area of ischemic damage and prevent leukocytes infiltration to the surrounding healthy tissue (93, 101). Both ischemic and hemorrhagic stroke cause brain edema, and astrocytes, through their unique ability to control water and electrolytes homeostasis, contrast the development of this health-threatening complications.

At the same time, several negative effects of astrogliosis have been documented, in particular in severe ischemic attack. Reactive astrocytes release MMP-2, causing degradation of BBB basement membrane proteins and ephrin-A5, with the latter involved in axonal sprouting and recovery after injury (137).

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C. Parkinson's disease: pathogenesis and main pathophysiological traits

PD is a progressive and disabling neurodegenerative disease that affects 2–3% of the population over 65 years (6, 91) of which the etiology is not well understood. PD is caused by the death of dopaminergic neurons (DA) in the substantia *nigra pars compacta* (SNpc), resulting in dopamine (DA) deficiency within the basal ganglia (91). Loss of DA leads to vast array of typical parkinsonian "motor" symptoms (73). The most credited pathogenesis theory suggest the role of a complex combination of genetic and environmental factors (73, 91). As for AD, the inherited type (due mutations in multiple distinct genes), is extremely rare, and presents a clinical phenotype very similar to the sporadic form (91). Lewy pathology is along with the loss of DAergic neurons within the SNpc, are not only well-recognized biological marker for the disease but also the main pathological hallmark (6, 91). A non-static role of Lewy pathology in PD development has also been suggested (91, 96). The emerging view is that this aberration might be transferred (by exocytosis of α-synuclein) from an affected neuron to a healthy neuron (4, 91). It was also observed that aggregation of misfolded α-synuclein led to decreases in synaptic proteins, and may drive neurodegeneration (200).

However, the causality of Lewy pathology in PD has not been firmly proven and some findings cast some doubts about its centrality in disease pathogenesis (91). Of particular relevance are the observations that Lewy pathology is absent in some forms of PD and that inclusions of other misfolded proteins could contribute to the clinical expression of PD (50, 91).

As exhaustively illustrated by Hirsch et al (91) alterations in mitochondrial bioenergetics (resulting in OxS elevation), dysregulation of calcium homeostasis, and neuroinflammation might synergistically play a role with the aforementioned neuropathological abnormalities in PD pathogenesis.

C.1. Neuroinflammation in Parkinson's disease

Published evidences have still not unraveled the exact impact of neuroinflammatory processes in PD pathology, and it remains to be clarified whether reactive gliosis promotes or protects from nigrostriatal pathway injury.

The most stringent argument supporting the involvement of neuroinflammation in PD was the detection of reactive microglia in the SNpc of human post-mortem brain tissue and in

that of PD animal models (56, 57, 120, 203). Positron emission tomography (PET) studies also demonstrated the presence of activated microglia in various regions of brain of PD patients (11). Further evidence was collected by analyzing the levels/expression of pro-inflammatory mediators. The results confirmed the increased levels of TNF-α, IL-1β and interferon-gamma (IFN-γ) in the ventricular CSF and in postmortem striata of PD patients (127, 203). This increase of pro-inflammatory mediators is particularly dangerous for the DA. Indeed, these neurons display much higher sensitivity to inflammatory stimuli to those of other regions of the brain (19). In addition, it has been shown that aggregated α-synuclein released from dying DAergic neurons can induce microglia towards M1 phenotype. Conversely, results from in vivo animal models suggest of own-regulation of M2 phase activation from microglia in the PD progression (146)

Thus, several lines of concordant preclinical evidence supporting the hypothesis that the microglia-mediated neuroinflammation contributes to the cascade of events that lead to degeneration and progression of PD (58, 99, 184, 213). Compelling data suggests that this contribution could be substantial since the early stage of the disease. Indeed Gerhard et al reported signs of sustained inflammation in various brain anatomical areas (including striatum) in PD patients (58). Relevant to this context are the recent “in vivo” data showing that overexpresses human α-syn is characterized by early neuroinflammation prior to the appearance of the classical signs of PD neurodegeneration (99).

D. Multiple sclerosis: pathogenesis and main pathophysiological traits

MS is a CNS chronic inflammatory and neurodegenerative disease with a supposed autoimmune origin, where CD4+ T cells orchestrate attacks to myelin sheaths and cells within the CNS (176). Although the etiology is still unknown, it is supposed to involve both genetic and environmental factors (65).

There are 3 main clinical subgroups of MS patients: relapsing-remitting (RRMS, almost 80% of cases), characterized by alternating phases of acute worsening of symptoms (relapse) followed by periods of recovery (remission) (68). Ultimately, as the disease progresses, the majority of patients undergo to a continuous deterioration in neurologic functions in the absence of relapses (secondary progressive MS, SPMS). Finally, almost 10-15% of patients present a primary progressive disease course (PPMS) characterized by a continuous neurological deterioration from the beginning (68).

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D.1 Neuroinflammation in Multiple sclerosis

Despite this heterogeneity in disease phenotypes, the neuropathology of MS involves both neuroinflammation and demyelination (68). Thus, at variance with the previously discussed neurological diseases where conclusive remarks are still awaited, in MS CNS inflammation is a certain and well-defined component.

Indeed, acute white matter demyelinating lesions show a substantial myelin breakdown accompanied by a massive infiltration of both innate and adaptive immune cells including macrophages, T and B lymphocytes (69), with a further involvement of local cells like microglia and astrocytes ultimately leading to gliosis.

Several in vivo studies mainly performed on the animal model of the disease, the experimental autoimmune encephalomyelitis (EAE), have revealed the prominent role of Th1 and Th17 cells in initiating inflammation within the CNS (68). However, before infiltrating the CNS, myelin-autoreactive T-helper cells need to be primed in the peripheral immune system, an event occurring within the lymph nodes in EAE but with still an unknown location in MS.

Currently, there are two main hypotheses for the role of the immune system in orchestrating the initiation and development of MS lesions. In the first major hypothesis, the activation of autoreactive immune cells by a still unknown CNS antigen occurs in the periphery and then transfer to CNS. Thus, the activation of immune cells in peripheral tissues (e.g. lungs, gut, skin) might be the result of cross-reactivity or molecular mimicry with self- antigens coming from the brain (176). Once activated and selected within lymph nodes, autoreactive T and B cells invade the CNS initiating the pre-phagocytic lesion development (69). Ultimately, the CD 4+ T cells infiltrating the CNS release several pro-inflammatory cytokines leading to the alteration of BBB permeability with the further influx of peripheral immune cells perpetuating tissue damage.

On the contrary, the second theory suggests that the initiating event occurs within the CNS, causing the subsequent activation of resident microglia which leads to the secondary recruitment of adaptive and innate immune cells (97).

Despite the theory, it is evident that one key step in MS pathogenesis is BBB impairment, an event occurring through the release of cytokines and chemokines upregulating adhesion molecules (122) (132), and MMPs, enzymes that degrade the basal lamina. In

particular MS patients have abnormally high production of MMPs, including MMP-2 and MMP-9, in both serum and CSF (191). In addition, activated CD4+ T cells are able to produce MMPs (169) thus stimulating both BBB breakdown and tissue damage (52). Once crossed the barrier, autoreactive CD4+ T cells are reactivated by the corresponding perivascular Antigen Presenting Cells (APCs) (12). This establishes the initial inflammatory site promoted by both the direct contact with resident immune cells (microglia, astrocytes and perivascular APCs) and the production of chemokines able to further recruit innate and adaptive immune cells from the periphery (132). Here, the main cells perpetuating the tissue damage seem to be microglia and infiltrating macrophages, since they are frequently found post-mortem around MS damaged axons (68). Notably, the main mechanisms by which activated phagocytes within the lesion can produce damage are: 1) the release of tissue destruction-promoting MMPs; 2) secretion of apoptosis inducing agents; 3) generation of ROS and RNS); 4) antibody-dependent cell-mediated cytotoxicity (132).

4. **From peripheral to brain inflammation**

At the current state of knowledge, the neurological diseases considered in this review are all characterized by an early damage of the BBB. Disruption of this physical barrier would lead to complete loss of the immune privilege of CNS, and the bidirectional transmission of pro-inflammatory signals would easily occur. One of the consequence of BBB breakdown is the migration of immune peripheral cells which has been identified as one of the major contributing factors for many neurodegenerative diseases (69, 89). For instance, immune cells such as CD4+ and CD8+ T lymphocytes, B lymphocytes, neutrophils and monocytes have been shown to play pivotal roles in both damage and repair processes after stroke (89). In PD, it has been shown that T- and B-lymphocytes infiltrates in the SNpc of α-synuclein overexpressing mice (3). In AD, it has been amply documented that peripheral monocytes play an important role in eliminating Aβ deposits from the brain parenchyma (187). As previously discussed, in MS peripheral T cells, B cells and macrophages infiltrated into the CNS act in concert to provoke the tissue damage (68). However, the entry of peripheral immune cells into the brain can be also considered an early event taking place before rupture of BBB (211). During neuroinflammation, inflammatory cytokines and attracting chemokines (such as CCL10 and CCL21) released from activated resident glial

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cells, lead to the activation of endothelial cells of the BBB (211). This increases the expression of adhesion molecules on endotheliocytes, facilitating the transmigration of activated peripheral immune cells expressing cognate ligands through the BBB (211). These events mutually concur to increase the permeability of BBB leading to the further entry of other systemic myeloid cells into the CNS, thus enhancing brain inflammation processes (211).

As discussed by elsewhere (27, 53, 76), the cross-talk between systemic circulation and CNS, and thus the possible interference of systemic inflammation on neuroinflammatory processes, can occur through many routes, that do not necessarily involve transmigration of blood-borne immune cells into the brain. These systems of communication have been demonstrated in vivo by using a direct peripheral challenge with the endotoxin lipopolysaccharide (LPS) or with pro-inflammatory cytokines, and further supported by human imaging studies (67). LPS, a key component of the outer membrane of gram-negative bacteria, is widely used to trigger the immune system and generate behavior changes, also known as 'sickness behavior' (13). Notably, following systemic challenge with IL-1β and TNF-α in mice, induction of cytokines in hippocampus is observed (172). However, in general, microglial response to peripheral inflammation is not related with a long-term neuronal damage. When the insult is acute, as following a brain ischemia, the microglia become activated and their response appears to be rapid and under control. In the case of a chronic and slowly progressive insult (as it occurs in AD and PD) the microglia do not become fully activated but primed. By definition, this microglial stage precedes a further neurotoxic activation as a consequence of secondary pro-inflammatory stimulus, coming from both periphery (cytokines) and brain (Aβ, Lewy body, OxS etc.). As a proof of concept, PD and AD patients and animal models with ongoing inflammatory neurodegeneration showed exacerbation of the neurodegeneration process after a peripheral inflammatory stimulus (53, 131).

The cytokines released by peripheral immune cells can enter the brain by exploiting an anatomical breach circumventricular organs, i.e. neural regions that are in contact with the cerebroventricular system (119). These structures have a rich vascular plexus with a lack of tight junctions between the endothelial cells and thus devoid of a BBB. Cytokines may also cross an intact BBB through active transport mediated by specific carriers. In both cases,

the acquisition of extra-CNS derived cytokines is deleterious for BBB integrity because they modify the resistance of tight junction of cerebral endothelial vessels (9, 119). Moreover, LPS or pro-inflammatory cytokines can lead to an activation of glial cells and perivascular macrophages, initiating and/or fueling neuroinflammation. Repercussions of peripheral inflammation on the brain can also stem from vagal stimulus (79) as rodent models suggested that vagus nerve is able to relay information to the brain about the body's inflammatory status, and in case of sustained systemic inflammation to increase the levels of brain cytokines (79).

Notably, the road that connect CNS with periphery has not only the direction that we have considered so far: indeed, the traffic is a two way road (53, 71). Acute brain injury elicits a systemic acute phase response and hepatic expression of chemokines, which in turn produce leukocyte mobilization and recruitment to both the CNS and the liver.

A. Preclinical evidence

Solid argument in favor of an implication of systemic inflammation in AD, VAD, PD and MS have been provided by animal studies investigating the effect of LPS injection on cognitive status and brain inflammation.

***Alzheimer's disease*:** Lee and coworkers found that LPS treatment negatively impacts memory function and accumulation of Aβ in the hippocampus and cerebral cortex of mice (90, 108). Another recent study has shown that LPS-induced sepsis upregulates Aβ levels (1–42) and p-tau, as well as increases the IL-1β, IL-6, and TNF-α and cortical microglial density (202)**.** Interestingly, the administration of a different systemic infection inducers, polyriboinosinic-polyribocytidilic acid (a synthetic analog of double-stranded RNA), led to similar consequences (100). Indeed, the induced systemic immune dysregulation during a late-gestational time was found to predispose offspring mice to typical neuropathology characteristic of sporadic AD. In particular, the induced increase in both circulating and brain IL-1β appear to activate and/or prime microglia, allowing an uncontrolled and exaggerated inflammatory response upon a secondary stimulus.

These data are concordant with evidence showing that injections of ectopic IL-1 entail elevation of APP production and amylodogenic cleavage (23), and increases in NFT (112).

Vascular dementia: Cerebrovascular disease was also demonstrated to be related with systemic inflammation (119). Systemic immune-dysregulation mimicked by IL-1 injection

led to stroke-related neuronal damage in mice model and this effect was mediated by proteolytic challenge against tight junction of BBB leakage (118, 119). This "corrosive" action was exerted in great part by MMP-9 released by leukocytes, and resulted in an unremitting increase in BBB permeability after experimental stroke (117).

Parkinson's disease: Prenatal exposure with LPS, leads to the birth of animals with lower number of DAergic neurons (30). The cell loss observed in these animals was accompanied by reduced striatal DAergic neurons and elevated DAergic activity, a physiopathological pattern that resembles that of PD patients and that leads to increase in neurotoxic ROS. The picture is completed by the observed increase of IL-1 and TNF-α in the CNS, which, especially for the latter, is maintained altered for the entire lifetime. This finding is important since TNF-α was found elevated in the brains of patients dying with PD (126). In vitro data obtained by the same group suggest that LPS induces the activation of microglia which, in turn, could be the source of life-time alteration of pro-inflammatory cytokines within the CNS, perpetuating DA loss and expression of PD brain characteristics (113). The neurotoxin 6-hydroxydopamine (6-OHDA) is widely used to induce models of PD, reproducing the main cellular processes involved in the disease, such as OxS, neurodegeneration, neuroinflammation, and neuronal death (72). Engler et al. demonstrated that the early phase after intrastriatal 6-OHDA administration is chiefly characterized by perturbation in peripheral immune system, which seems to be related with the neurodegenerative process observed in treated animals (51). Notably, employing IL-1β as peripheral stimulus in 6OHDA animal model leads to an increase in neurodegeneration (148).

Multiple sclerosis: Most of the evidence regarding key events of MS pathogenesis and involvement of systemic inflammation in MS comes from murine models. Systemic administration of LPS to EAE rats is able to induce lesion reactivation in the brain as evidenced by magnetic resonance imaging (MRI) and increased leukocyte infiltration as well (162). Other clues of a two ways systemic-CNS cross-talk are represented by studies on MS peripheral blood mononuclear cells, confirming an increased production of pro-inflammatory cytokines during acute attacks compared with recovery phase (75). The same has also been confirmed by in vivo results suggesting that systemic inflammation is strongly associated with periods of intense relapses (41).

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B. Clinical/epidemiological evidence

The most striking proofs linking the neurological diseases dealt with in this review and systemic inflammation come from studies exploring peripheral markers of this physiopathological condition. The enormous amount of epidemiological evidence related to this topic are well summarized and highlighted in dedicated meta-analysis and systemic reviews, which will be the major sources of data discussed in this paragraph.

Alzheimer's disease and vascular dementia : One of the first study with meta-analysis approach reported a significant increased risk of all cause dementia for individuals with higher level of C-reactive protein (CRP) and IL-6 (98). The authors underpinned that this association was mostly driven by VAD, since both markers are well-established predictors of CVD, major risk factor and comorbidity for this form of dementia. Likewise, a meta-analysis on prospective studies found that CRP, IL-6, a1-AT, Lp-PLA2 activity, and fibrinogen are associated with the risk of all-cause dementia, while these inflammatory markers resulted nonspecific for AD (43), as also suggested by other authors (133). In contrast with these findings, the study by Tao et al. on 2656 members of Framingham Heart Study offspring reported that the presence of systemic inflammation was associated with brain atrophy and shortened the latency for developing AD (185). Further, a meta-analysis on higher number of studies (33 344 AD and 12 912 healthy controls) reported elevated levels of many pro-inflammatory markers (IL-1β, TNF)-α-2, IL-6, IL-18) in association with AD, with IL-6 levels inversely correlated with mean MMSE scores (104).

Parkinson's disease: Convergent evidence linking systemic inflammation and PD have been reported. In particular, a recent meta-analysis on 25 studies revealed increased levels of IL-6, TNF-α, IL-1β, IL-2, IL-10, CRP, and RANTES in patients with PD (151). IL-6, TNF-α and PCR have been also shown to relate with severity or faster decline of motor symptoms (209). Consistent findings also emerged from Genome-wide studies that revealed several polymorphisms in inflammatory genes associated with PD (64). Intriguingly, patients with inflammatory bowel disease have a higher incidence of PD, which is substantially attenuated by anti-inflammatory treatment (143).

Multiple sclerosis: Patients with RRMS are characterized by an increased serum concentration of the Th1 cytokine, IFN-γ (92). The same was also observed for other markers of inflammation, the Th17 cytokines, which are postulated to be strictly

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connected with the disease. Indeed, a recent meta-analysis found that serum IL-17 and IL-23 concentrations are increased in MS patients (111). In addition, serum levels of other non-classical inflammatory markers, such as osteopontin (OPN), have been found increased in MS. Interestingly, this systemic increase was suggested to be mirrored also in the CNS, as highlighted by the high levels of OPN found in the CSF of MS patients (1). However, the most important results come from Bai et al. that analyzed the data from 226 studies including more than 13,000 MS patients and 8,000 controls (8). The authors found increased levels of 21 cytokines in the blood and 13 cytokines in the CSF of MS patients compared to controls (for a complete list, see the work from Bai et al. (8)). In addition, some of them were increased in both CSF and blood suggesting a common unbalanced inflammatory response involving CNS and periphery as well.

5. Sources of systemic inflammation in Alzheimer's disease, vascular dementia, Parkinson's disease, and multiple sclerosis

A. Metabolic factors:

Alzheimer's disease and vascular dementia: It is well recognized that obesity related metabolic alterations and disease, such as Type II diabetes mellitus (T2DM), dyslipidemia, metabolic syndrome and CVD are strong risk factor for VAD, and for AD. In particular, high body mass (BMI) or waist circumference in midlife, often result of scarce physical activity (other risk factor for dementia), are related with structural brain changes, increased cognitive decline and AD in late life. Larger abdominal circumference was found to correlate with decreased hippocampal volume and much higher risk of developing AD, when compared with those with the smallest diameter (84, 207).

The observed association between obesity and cognitive decline could be explained by chronic subclinical systemic inflammation that is caused by excess of adiposity, especially in abdominal/visceral depot. Obesity-associated low-grade inflammation appears to originate primarily from macrophage infiltration in adipose tissue. This perturbation in immune homeostasis is also causative of insulin resistance and chronic hyperglycemic state, typical metabolic complication of obesity. As already mentioned, diabetes is one of the major risk factors for AD and the mechanistic linking these two diseases may involve, besides inflammation, brain insulin resistance (106), hypercholesterolemia (cholesterol increase β-secretase activity) and mitochondrial dysfunction (168, 180).

Parkinson's disease: The association between obesity, dyslipidemia, diabetes and PD has been also investigated and the results published so far appear controversial. A recent meta-analysis showed that overweight people have a higher risk of being affected by PD. Quite surprisingly, the authors reported that obese people, did not exhibit a significant relative risk for the neurological disease (39). In this context, negative results come from a large prospective study on 121,879 subjects, showing that PD was not significantly related to history of hypertension, hypercholesterolemia, or diabetes (166). In contrast, a more recent meta-analysis dealing with over 1,761,000 individuals, has showed that, compared to nondiabetic patients, patients with diabetes were associated with a 38% increase in the risk of developing PD.

Multiple sclerosis: The possible association between diabetes and MS has been observed for more than 15 years. However, all the current clinical evidence comes from studies regarding T1DM, where it has been proposed that the two disease share a common, though not fully disclosed, immune pathogenetic mechanism (activation of autoreactive CD4+ T cells, migration within the islets, infiltration of peripheral macrophages, tissue damage) (24, 130). Despite this long known tentative connection, information about the possible MS risk modulation by T2DM are still scarce. In the only large population-based study found in literature on this matter (77), the authors reported that T2DM was significantly associated with an increased risk of MS, a relationship probably confounded by age and sex (77). Nonetheless, the missing link between the two diseases is still unknown although it has been hypothesized that immunity and environment in the context of T2DM may interact to increase MS susceptibility.

B. Infections

The already commented results obtained with experiments with systemic injection of LPS, have been interpreted as a clue of a possible causal role systemic infection in PD and AD.

Alzheimer's disease: Over the past three decades, infectious agents such as bacteria, viruses, fungi, and protozoa have been reported to trig the development of AD. The proposed intriguing concept that amyloid might act as an antimicrobial peptide in the brain has sparked intense research on the topic.

Accordingly, a survey of 1,194 patients with more than one hospitalizations for infection with severe sepsis, showed that sepsis survivors were at higher risk of persistent cognitive

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decline impairment and functional disability, compared to survivors experiencing non-sepsis hospitalization (83). The connection between cognitive dysfunction and sepsis has been well substantiated by preclinical evidence, and appears to be mediated by systemic inflammation. Indeed, as also underscored earlier, this acute event following dysregulated host immune response after infection induces the release of pro-inflammatory cytokines that exacerbates the accumulation of Aβ and triggers AD progression (60). As demonstrated in several experimental model, a compromised BBB is one of the consequences after bacterial and viral infections.

Among infectious pathogens linked to AD onset and progression are the spirochetes family and periodontal pathogens such as *Porphyromonas gingivalis* or *Treponema denticola* that could cause chronic periodontitis (175).

Parkinson's disease: A growing number of bacterial and viral pathogens have been associated with PD risk. As suggested by Johnson et al, these microorganisms could be ascribed as potential triggers of the disease (88) that cannot cause by their self the cascade of aberrant events leading to PD development, but need "facilitator", such as systemic inflammation. Hepatitis B and C, *Norovirus* and M. *paratuberculosi*s have been suggested as possible causative factor of PD. In particular, it has been observed that gastrointestinal infection by Norovirus induce upregulation of α-synuclein in the gastrointestinal tract (103). The presence of systemic inflammation, might exacerbate the α-synuclein aggregates and allow for their diffusion through the *vagus* nerve, finally leading to Lewy pathology in the CNS (178).

Multiple sclerosis: As strongly reported, one of the hypothesis for the MS etiological factor is the involvement of the so called "molecular mimicry" of antigens belonging to viruses that resemble myelin peptides (68). In particular, several works postulated that *Epstein-Barr Virus* (EBV), a human herpes virus, plays a dual role by increasing the risk of developing MS and contributing to the pathogenesis either directly or indirectly by activating silent infections (63). However, a clear association between this virus and the disease still needs confirmation. Nonetheless, apart from EBV other works found, at different levels, that systemic infections are able to trigger MS relapses in humans as observed in the preclinical model (161). Indeed, the epidemiological observation of increased relapse frequency associated with a raise in adenovirus antibody titers (5),

urinary (121) or bacterial infection (152) together confirm the strict influence of the peripheral immune system response on central neurodegeneration.

C. Microbiota dysbiosis

The gut microbiota comprises a complex community of microorganism residing in our gastrointestinal ecosystem. Evidence links perturbations in the gut microbiota (microbiota dysbiosis) to neurological disease, including disease risk, activity, and progression. A growing body of literature has focused on illuminating the bidirectional communication pathways between gut bacteria and the CNS: gut–brain axis. The mechanisms underlying the association between gut microbiota and neurological diseases is still partially unknown, and seems to involve (among the others) systemic inflammation. The gut microbiota greatly influences the shape and quality of the immune system (20). During chronic intestinal inflammation, loss of intestinal barrier function results in leakage of bacteria and endotoxins into the circulation promoting the release of proinflammatory cytokines and chemokines by Th17 and B cells (20). Release in circulation of endotoxins and proinflmmatory amyloids and lipopolysaccharides, could also take place in the absence of breakdown of intestinal barrier, as it occurs in microbiota dysbiosis (42, 86, 188).

Alzheimer's disease: Gut bacteria such *as Escherichia and Shigella* have been found to be at higher amount in fecal samples from AD patients compared with cognitively normal subjects (32). Of note, the increased abundance of these proinflammatory bacteria was observed in combination with a decrease of anti-inflammatory *Escherichia rectale*, and increase in circulating proinflammatory cytokine levels (32). Consistent with these patients findings, AD animal models exhibited altered microbiota, and treatment with an antibiotic cocktail reduced microglia and astrocyte accumulation around amyloid plaques in the hippocampus, and decreased Aβ plaques (124) .

***Vascular dementia*:** The study on the effects of dysbiosis in two different animal model for stroke were conducted by Singh et al. (170) and they found that changes in the gut microbiota affected neuroinflammatory and functional outcomes after brain injury. In support of these finding, the administration of antibiotics in the mouse model of experimental stroke before cerebral ischemia is related with worse outcomes in mice (210)

. This antibiotic effect might be related to a reduction in the trafficking of proinflammatory cells and alteration in chemokines expression (17).

Considering epidemiological evidence, the association between atherosclerosis and hypertension, well-established risk factors in cerebrovascular disease and stroke, and microbiota richness and diversity is now widely recognized (110).

***Parkinson's disease*:** The discovery that α-Synuclein is also present in the mucosal nerves and ganglia of patients with parkinsonian syndrome and the evidence that α-synuclein in the gut can be transported to the brain via the vagus nerve, led to the idea that this pathology may origin from gut (42, 157). Although this hypothesis lacks of definitive confirmation, the influence of alterations in the composition of the microbiota in PD onset and progression appears more solidly supported (88, 179).

Multiple sclerosis: The hypothesis of a prodromal role of microbiota in MS found support from a clinical study investigating microbiota profiles in early onset pediatric MS and control children (189). The authors reported a significant difference in the gut microbiome composition between the two groups, with perturbations observed in MS children suggesting a shift towards a proinflammatory environment already observed in other autoimmune diseases (158). Moreover, another study identified specific bacterial taxa in MS patients associated with an increase of proinflammatory responses in human PBMCs (33). Of interest, the authors also reported that microbiota transplants from MS patients into germ-free mice resulted in more severe symptoms of EAE compared with mice "humanized" with microbiota from healthy controls (33).

D. Oxidative stress

D.1. **Oxidative stress and inflammation cross-talk**

In authors' view, the most accurate and exhaustive definition of OxS has been formulated by the Helmut Sies, a landmark in the field of redox biology, who describes the condition as "as an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage" (165). In line with this definition, low exposure with oxidants is of crucial importance for living organisms, because redox signaling regulated specific components of cell metabolism, controlling cell growth, differentiation, and death. On the contrary, an excessive oxidative challenge coupled with an inadequate feedback response by antioxidant defensive mechanisms,

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results is an alteration of the cellular redox homeostasis leading eventually to permanent damage (165). Inflammation is ascribed as one of the endogenous stressor that is potentially able to derange redox homeostasis, leading to the uncontrolled production of oxidants such as ROS and RNS (196). On the other hand, inflammation has always been linked to oxidative stress although it is very difficult to extrapolate the cause and the effect in this cross-talk.

Indeed, OxS has a tight relationship with inflammation, as the two processes are often interconnected (59, 138). In the course of an inflammatory event, oxidants can be generated by defects in mitochondrial respiratory chain, abnormal catalysis of enzymes as well as from non-enzymatic reaction catalyzed by transition metals (25, 44, 198). A striking example in this frame is given by Nicotinamide Adenine Dinucleotide Phosphate Oxidases (NOXs) that, upon stimulation by TNF-α and IL-1β, releases high concentrations of ROS (46, 107, 206). Excess of NOX derived superoxide, resulting from a sustained proinflammatory stimulation, inevitably causes tissue injury and exacerbates inflammation (46, 196). This vicious cycle is fueled also in the absence of biological damage, since increase in ROS can upregulate cellular inflammation pathways such as protein kinase cascade (PKC, MAPKs etc.) and activate transcription factors (primarily NFAT-1, AP-1, HIF-1α, and NF-kB) that are able to initiate and/or reinforce inflammation (125, 129, 196). NOX and mitochondria-derived ROS are required for respiratory burst occurring in activated leukocytes, that in turn, leads to a systemic increase of oxidative damage to biomolecules (28, 87). A similar attitude to translate an inflammatory signal into oxidant production is possessed by Myeloperoxidase, an heme-peroxidase mainly produced by granulocytes and monocytes with an important role as a first line defense against microbial infections (78). If stimulated, this enzyme, in cooperation with NOX, is able to catalyze the formation of great amount of reactive species, hypohalous and (pseudo) hypohalous acids (29).

D.2. The vicious cycle between oxidative stress and inflammation in neurological diseases

The detrimental self-perpetuating cycle involving OxS and inflammation and reflecting in both brain and periphery clearly emerged as a common mechanism underlying the pathogenesis of AD, VAD, PD and MS. Indeed, in these diseases, the already discussed widespread inflammatory signatures are accompanied by particularly high levels of

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oxidized lipids, proteins and carbohydrates with low levels/activity of molecules with antioxidative proprieties in the brain, CSF and peripheral fluid (10, 31, 36, 54, 82, 149, 217).

Brain is highly susceptible to oxidative damage for many reasons, as elegantly discussed by Cobley et al (40). The modest content in antioxidant enzyme system, *e.g.* catalase, and the low-molecular-weight antioxidants, e.g. glutathione (GSH), relative to many tissues (e.g. liver) represents one of most important reasons underlying this anomalous vulnerability (major mechanistic details in (14)). Moreover, the brain is the major sink for polyunsaturated n-3 fatty acids, notably docosahexaenoic acid (DHA) (15). Despite the great demand of energy and the high amount of phospholipids, the neurons obtain low ATP from lipid beta-oxidation (40). These non-metabolized polyunsaturated lipids, are preferential targets of highly reactive hydroxyl or peroxyl radical (brain is also enriched in transition metals, i.e. Fe^{2+} and Cu^{+}, that give rise to these radicals through Fenton reaction), which trigger lipid peroxidation, resulting in neuron damage (36, 40). Some of the products of lipid peroxidation, e.g. F(2)-isoprostanes, malondialdehyde, 4-hydroxy 2-nonenal (HNE), are well-accepted biomarkers of OxS (49, 195). These molecules are not merely “static” indicators, but act as mediator and propagator of oxidative damage. HNE represents one of the major aldehydic end-product stemming from peroxidation of biomembranes, and is able to form covalent adducts with proteins and nucleic acid leading to marked change in their structure/function (49). Increased levels of HNE-protein adducts have been found in the brain and in body fluids of subjects affected by AD, PD, and other neurological diseases (49, 116, 159). Pathological levels of HNE enhances Aβ production, tau phosphorylation, damage or kill primary hippocampus neurons, but also induces and/or sustain inflammation and causes vascular abnormalities (49, 147). High levels of HNE was also found to alter DA transport contributing to the loss of this neurotransmitter and causes nigral cell death (47).

Due to the indissoluble and reciprocal link between OxS and inflammation, discerning which one is cause or effect is almost impossible. OxS has been ascribed, although not unanimously, as a primary pathogenic trigger in AD (38) as well as a major contributor to the development and clinical progression of the other 3 diseases (36, 109, 136, 197).

As anticipated, in AD, a non-physiological increase in superoxide radical ($O_2^{\bullet -}$) and the mild oxidant, hydrogen peroxide (H_2O_2), due to mitochondrial dysfunction has been proposed to precede the appearance of the well-established neuropathological hallmarks, Aβ and NFT (134, 212). One of the mechanism linking mitochondrial defects and AD onset, comes from animal experiments showing that the activity of β-secretase, rate-limiting step of amylodogenic process, is highly increased in the presence of ROS (182). A significant increase of these species has been also described as a possible mediator of neurotoxic effects of Aβ and NFT (204). In particular, Aβ appears to be the main source of free radical production via Fenton reaction oxidation of APP (2). Consistently with this hypothesis, increased iron contents have been found in Aβ and NFTs deposits, with the latter that is also able to boost up the metal ions capacity to generate reactive species. However, this neurotoxicity can also be due to proinflammatory cytokines and chemokines released, together with NOX-generated superoxide radical, from microglia upon respiratory burst induced by exposure to Aβ (26).

Within the vessel wall, high levels of superoxide radical produced by endothelial NOX or by uncoupled endothelial nitric oxidase, induce structural and functional changes that have broad implications for regulation of cerebral perfusion and permeability of the BBB (102, 217). These OxS-induced changes are thought to contribute to the progression of cerebrovascular diseases (102).

In PD, DA can be a major source of OxS. Excess of cytosolic DA, is easily oxidized both spontaneously and enzymatically to produce DA quinone. (80). Then, the formed DA quinone species are capable of modifying a series of proteins implicated in PD development, including α-synuclein and components of mitochondrial respiratory chain, leading to increase in ROS production (80). Moreover, this quinone can cyclize to become the highly reactive aminochrome, whose redox-cycling causes the formation of superoxide radical

Oxidative injury is also involved in cell degeneration in all stages of MS. Indeed, OxS-related damage to biomolecules is involved in both demyelination and axonal damage (136). These damaging factors are mainly produced by resident activated microglia and infiltrating macrophages, although a major role is played by transition metals like iron (177). However, an increased OxS is not only present during symptoms exacerbation.

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Indeed, recent studies found an increased systemic levels of oxidative damage markers in MS patients compared to controls (171) irrespective of the disease phase, relapse or remission, of the patients (34, 190). These data suggest that chronic systemic OxS is a relevant pathogenic phenomenon also at systemic level and not confined to CNS.

However, although OxS is one of the primary factors of cell injury in the aging CNS and chronic inflammation, during the repair processes of damaged nervous tissue a cascade of side effects occurs that affects the excessive production by phagocytes, inflammatory cytokines, and ROS, as well as RNS.

In summary, OxS emerge as a common systemic and brain abnormality in AD, VAD, PD and MS, and this could be one factor accounting for the cross-talk between peripheral and CNS inflammation.

D.3. Antioxidant supplementation in Alzheimer's disease, Vascular dementia, Parkinson's disease and multiple Sclerosis

The existing therapeutic options for the neurological diseases considered in this review, are largely limited to delayed disease progression and ease of symptom burden, albeit without modification of disease-course. This has sparked the demand of alternative therapeutic strategies, including antioxidant supplementation, able to prevent or delay the onset of the diseases. The rationale for this type of interventions came from the aforementioned antioxidant deficiency that reportedly characterized both periphery and brain of affected patients (36, 94, 160)

Great efforts in this direction have been mostly made for AD, with a major focus on the effect of α-tocopherol and ascorbic acid (145). As exhaustively reviewed elsewhere no clinical trials clearly demonstrate that a specific antioxidant intervention could be effective in AD (22, 128). It is epidemiologically proven, however, that a diet rich in fruits and vegetables rich could if not prevented at least delay the onset of AD (199).

Disappointing outcomes have been also obtained by clinical trials with antioxidants (such as α-tocopherol, ascorbic acid, β carotene, and coenzyme Q10) in PD (205). Relevant in this framework, DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism), a large, prospective, randomized trial unequivocally showed that α-tocopherol fails to delay the onset of disability associated with early, otherwise untreated PD (218). Finally, also the

clinical effectiveness of antioxidant supplementation as complementary treatment against MS onset, progression or symptomatology has to be still clearly proven (193).

Thus, the issue of whether antioxidant treatment is of use in neurological diseases is not settled and the available published results are clearly negative. Novel robust clinical studies on larger population-sample, possibly implemented with the measurement of antioxidant and oxidative damage biomarkers, is warranted to definitively clarify this point.

6. Conclusion

The main intent of this review was to summarize and discuss the most convincing preclinical and clinical evidences in support of the idea that systemic inflammation plays a role in the development of AD, VAD, PD and SM. These convergent evidences give the rationale for alternative pharmacological and/or non-pharmacological treatments for these diseases. Targets of these interventions are the potential sources of peripheral inflammation, such as metabolic conditions and diseases, perturbations of microbiota, OxS. Avoiding systemic inflammation caused by any pathogens or chronic pathological conditions able to stimulate immune system, from the common flu virus to the typical elderly-related such as chronic obstructive pulmonary disease, could be an additional therapeutic approach to apply in combination to the current used therapies.

Innovation:

Alzheimer's disease, vascular dementia, Parkinson's disease and multiple sclerosis, though having different neuropathological traits and clinical presentation, share several common features: 1) neuro-inflammation plays a role in the pathogenesis 2) systemic inflammation impacts brain inflammation and influence the pathological trajectory 3) infections, metabolic abnormalities, Microbiota dysbiosis, oxidative stress are sources of systemic/brain inflammation in these diseases.

Preventing and/or treating these "systemic abnormalities" could have beneficial effects on the these neurological diseases

Acknowledgements

We thank Dr. Valentina Gentili for her precious assistance in drawing the manuscript's illustrations

Author Disclosure Statement

No competing financial interests exist for any authors of this manuscript

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Abbreviations:

Activator protein-1, AP-1

Amyloid-β, Aβ

Amyloid precursor protein, APP

Alzheimer's disease, AD

Cerebrospinal fluid, CSF

Cerebrovascular endothelial cells, CerEC

Dopaminergic neurons, DA

Epstein-Barr Virus, EBV

Glial fibrillary acidic protein, GFAP

Interleukin, IL

Intermediate filaments, IFs

Lipopolysaccharide, LPS

Metalloproteinase, MMP

Mitogen-activated protein kinase, MAPK

Multiple Sclerosis, MS

Neurotoxin 6-hydroxydopamine, 6-OHDA

Nicotinamide Adenine Dinucleotide Phosphate Oxidase, NOX

Nitric oxide, NO

Nonsteroidal anti-inflammatory drug, NSAID

Neurofibrillary tangles, NFT

Nuclear factor of activated T cells, NFAT

Nuclear factor κ B, NF-κB

Osteopontin, OPN

Primary progressive multiple sclerosis, PPMS

Receptor for advanced glycation end products, RAGE

Signal transducer and activator of transcription 3, STAT3

Substantia nigra pars compacta, SNpc

Secondary progressive MS, SPMS

Parkinson's disease, PD

Toll-like receptors, TLRs

Triggering receptor expressed on myeloid cells 2 (TREM2)

Tumor necrosis factor-α, TNF-α

Oxidative stress, OxS

Vascular dementia; VAD

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Inflammation in neurological disorders: the thin boundary between brain and periphery (DOI: 10.1089/ars.2020.8076)

Figure legends

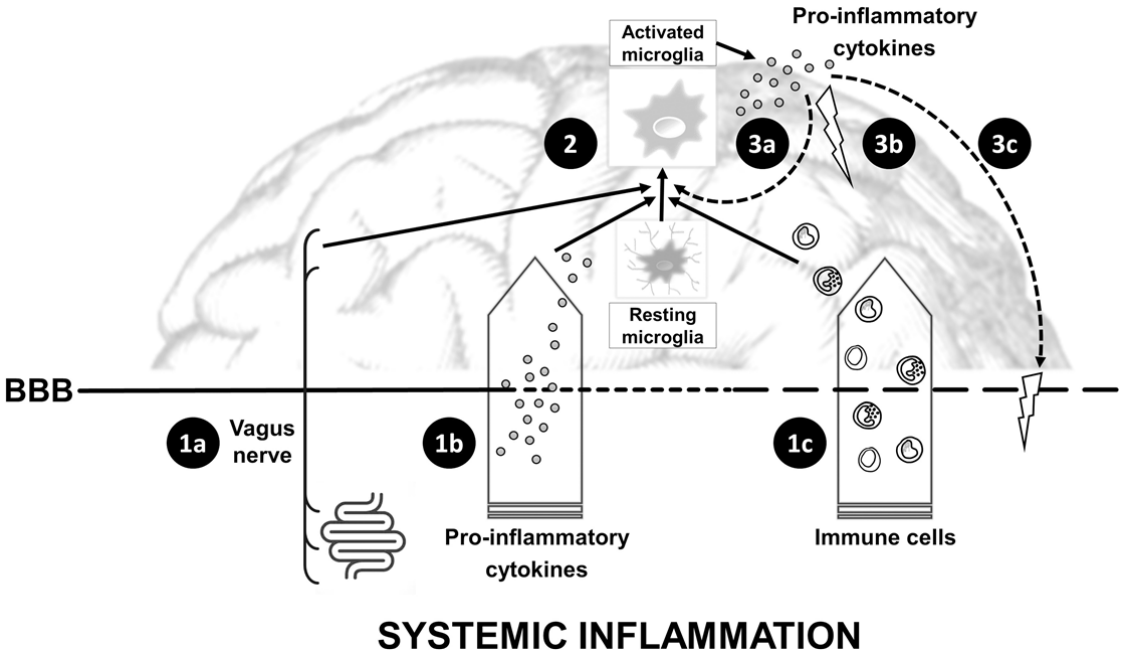

Fig. 1 Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease (PD) and multiple sclerosis (MS): from neuropathological abnormalities to neuroinflammation. **(1)** The typical neuropathological hallmarks of AD (Aβ and NFT), VAD (brain hypoperfusion, hypoxia, stroke), PD (aggregation of misfolded α-synuclein), and MS (demyelinating lesions, immune cells infiltration) are able to induce microglia activation (**(2)→ (3)**). **(4)** The consequent release of pro-inflammatory cytokines (in primis, Il-1β and TNF-α) and reactive species can lead to neuronal/axon damage (**(5a)**) and/or exacerbate the neurotoxicity and pro-inflammatory stimuli of the neuropathological abnormalities (**(5b)**). Abbreviations: Aβ, Amyloid-β; IL, interleukin; NFT, neurofibrillary tangles; ROS, reactive oxygen species; RNS, reactive nitrogen species; TNF-α, Tumor necrosis factor-α.

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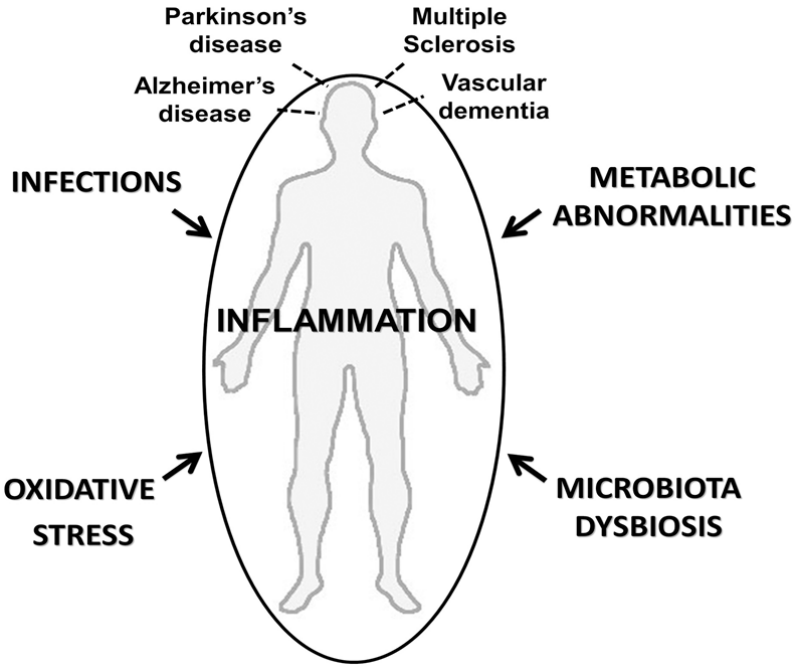

Fig. 2 Possible routes through which systemic inflammation influences brain inflammatory processes.

The cross-talk between systemic circulation and CNS, and thus the influence of systemic inflammation on neuroinflammatory processes, can occur through different routes: **1a)** vagus nerve that is able to relay information to the brain about the body's inflammatory status (103) **1b)** peripheral cytokines that can cross BBB exploiting brain structures that lack the normal BBB, i.e. circumventricular organs (101), or specific carriers (101, 102) **1c)** transmigration of blood-borne immune cells into the brain through a partially or totally damaged BBB (82, 83, 91, 92, 93, 94). All these challenges lead to the activation of microglia (**2)**) and, as effect, the onset or the exacerbation, of neuroinflammation. The release of pro-inflammatory cytokines, chemiokines and reactive species from reactive microglia give rise to a vicious cycle characterized by **3a)** increase in the number of activated microglia **3b)** damage of neuronal tissue **3c)** damage of BBB (thus leading to the further entry of other systemic myeloid cells into the CNS).

Abbreviations: BBB, blood brain barrier

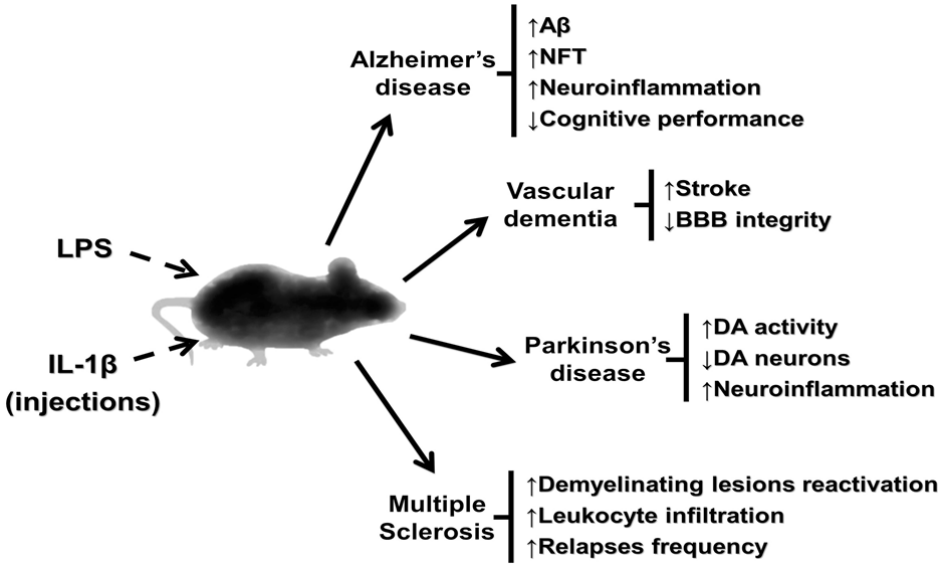

Fig.3 Implication of systemic inflammation in the onset/progression of Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease (PD) and multiple sclerosis (MS): PRECLINICAL EVIDENCE

The most documented effects of systemic challenge with lipopolysaccharide (LPS) or IL-1β (or TNF-α) to the respective disease-animal models are the following: 1) *AD:* memory function impairment (103,104); accumulation of Aβ in the hippocampus and cerebral cortex (103,104); increases in NFT (109); increases the IL-1β, IL-6, and TNF-α and cortical microglial density (106, 107). 2) *VAD*: stroke-related neuronal damage (101, 110); increase in BBB permeability (111). 3) *PD*: reduced number of DA neurons and increase in DA activity (following prenatal exposure with LPS) (112); increase of IL-1 and TNF-α in the CNS (113, 114). 4) *MS:* increase in demyelinating lesion reactivation (118); increase in disease relapses (119, 120); increase in leukocyte infiltration (118). Abbreviations: Aβ, Amyloid-β; BBB, blood brain barrier; DA, Dopaminergic; IL, interleukin; NFT, neurofibrillary tangles

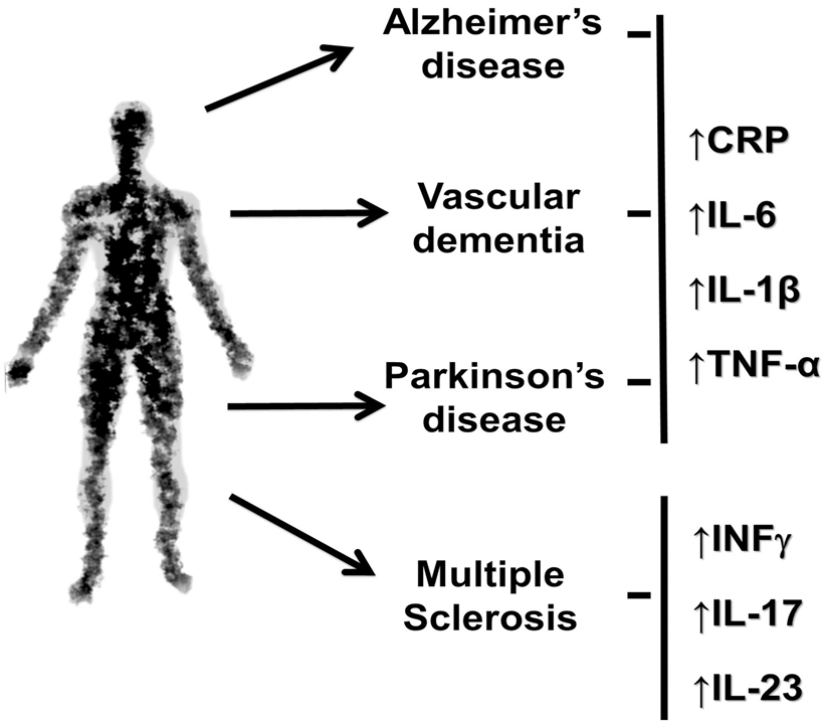

Fig.4 Implication of systemic inflammation in the onset/progression of Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease (PD) and multiple sclerosis (MS): EPIDEMIOLOGICAL/CLINICAL EVIDENCE.

The relationship between AD, VAD, PD, and MS and systemic inflammation is well supported by comprehensive meta-analysis focusing on inflammatory markers evaluated in patients of affected patients. In the Figure, we have shown the peripheral mediators/markers that have been more reliably found to be associated with the aforementioned diseases. See the references in the main text.

Abbreviations: IL, interleukin; TNF-α, Tumor necrosis factor-α, NFT; CRP, C-reactive protein; INF, interferon

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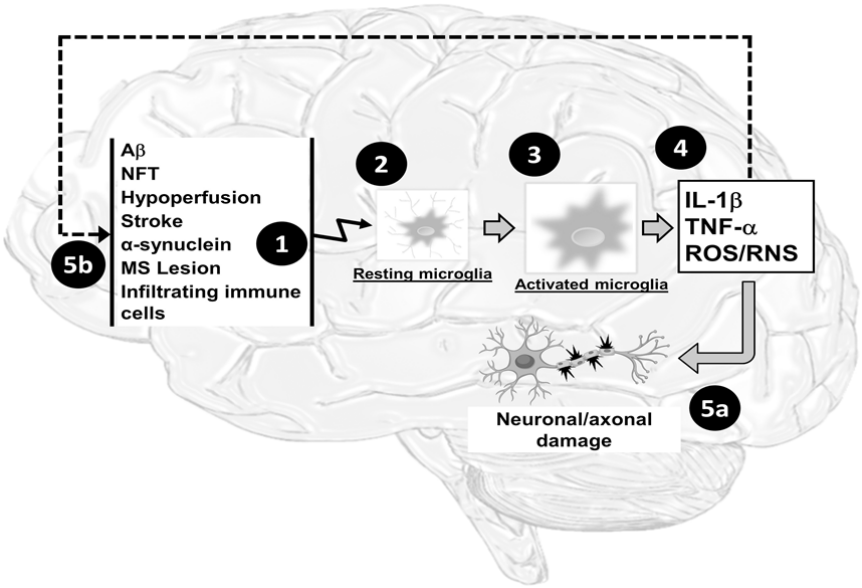

Fig. 5 Sources of systemic inflammation in Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease (PD) and multiple sclerosis (MS)

The most likely sources of systemic inflammation associated to AD, VAD, PD and MS are: infections by bacteria and virus; metabolic alterations and diseases (diabetes, obesity, dyslipidemia etc.); perturbations in gut microbioma; oxidative stress and inflammation generate a self-perpetuating cycle, which reflects in both brain and periphery.