Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis

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Abstract

In order to better understand the pathogenesis of Parkinson's Disease (PD) it is mandatory to "put it into the aging process", as aging is the most important risk factor for such a neurodegenerative pathology. Accordingly, we argue that a major mechanism underlying PD is inflammaging, *i.e.* the chronic inflammatory process characterized by an unbalance between pro- and anti-inflammatory stimuli, which is recognized a major component of most age-related diseases, including neurodegenerative diseases. A recent conceptualization suggests that inflammaging is part of the complex adaptive mechanisms ("remodelling") that continuously occurs lifelong to neutralize the endogenously-produced danger signals (molecular "self-garbage", including compounds/bacteria from gut microbiota) which fuel inflammaging, and can propagate inflammation locally (from cell to cell) and systemically (via exosomes and other molecules present in the blood of old subjects). Overall, this scenario is compatible with the hypothesis that inflammaging is an hormetic adaptation which is fundamental for survival but become detrimental in the post-reproductive period of life. Within this perspective, new treatments of PD can be envisaged, based on compounds capable of exerting hormetic effects switching the above-mentioned balance toward anti-inflammatory responses, including strategies capable of modulating the gut microbiota.

Aging, inflammaging and neuroinflammation

The phenotype of old people is the result of the body to respond/adapt to cellular and molecular insults continuously in all tissues and organs (damaging stimuli) we are exposed to lifelong, which are sensed as danger signals recognized by a limited number of evolutionary conserved receptors. This phenomenon has been conceptualized as "remodelling", which can be considered a general theory of aging [1,2].

The exposure to danger signals is a physiological phenomen (occurring in all organisms, including the young), which stimulates concomitant local and systemic responses, including the activation of the innate immune system, which can be conceptualized as "physiological inflammation", a concept first proposed by E. Metchnikof more than a century ago. Such an inflammatory response, which we can reformulate as "inflammatory tone", is highly conserved in evolution and critical for survival. Within this theoretical framework, the progressive increase with age of the inflammatory tone, resulting from a global increase in the sources/production of danger signals was conceptualized as an important example of remodeling and was dubbed "inflammaging" [3,4].

Recently it was established that both systemic inflammation and neuroinflammation are current in the prodromal phase and sustained in the development of PD. Scientific data report that the peripheral immune system is activated and aggravates the brain inflammatory response, which may begin or increase neurodegenerative processes. In the central nervous system (CNS) an acute insult stimulates activation of microglial that increased and promote the recruitment of peripheral leukocytes to the CNS. This inflammatory process showed two different peculiarities; it is beneficial for neuronal tissue, since it stimulates clearance of cell debris and secretion of several neurotrophic factors; but conversely, inflammatory mediators modulate immune cells and act on neurons and contribute to neurodegenerative alterations [5]. In this contex the activation of inflammatory responses is fundamental for tissue homeostasis but can contribute to neuronal injury in particular when it is not monitored or it is in a chronic state. The CNS is composed of neural tissues with a regenerative capacity and for this reason it is particularly vulnerable to uncontrolled immune and inflammatory alterations [6]. Primarily the CNS was considered a privileged immunologically organ, a property that has been assigned to the presence of the blood-brain barrier (BBB), the low expression of major histocompatibility complex class II (MHCII) and the lack of brain lymphatic vessels; this point of view

changed after identification of inflammatory and immune mediators in patients with neurodegenerative diseases.

The BBB is a cellular barrier between CNS capillaries and extracellular fluid of neurons and glial cells. The main function of the BBB is to provide a stable microenvironment for neural function, by providing optimal concentrations of ions for neural communication, due to the functional combination of channels and transporters of specific ions; furthermore, while the peripheral nervous system and CNS utilize the same neurotransmitters, the BBB prevents their free flow and sustains ~~the~~ optimized concentrations to avoid excitotoxicity phenomena. CNS pathologies and neurodegenerative diseases enhance BBB dysfunction **(Fig.1).** An increased BBB permeability promotes entry of macromolecules into the CNS and changes in blood vessels. This conclusion indicates that several neurodegenerative diseases are affected by the breakdown of the blood-brain barrier, leading to infiltration of inflammatory and immune mediators from the periphery. Recently, in this context, Louveau and colleagues demonstrated the presence in mouse brain of lymphatic vessels [7]. These data support the possibility of a new mechanism of entry and exit of immune cells from the CNS into the periphery aside from blood-brain barrier breakdown with implications in human neurodegenerative diseases. With the study of immune defense mechanisms from invertebrates to vertebrates, including humans, emerged the macrophage as the central player in this evolutionary scenario, not only for its role in inflammatory response and innate immunity but also in the stress response [8]. Indeed, on the basis of findings on the common evolution of immune and neuro-endocrine responses, we proposed the unifying term “stressors” to embrace all types of danger stimuli, including “antigens” and cell debris, capable of stimulating/activate the macrophage. Recently, inflammaging was recognized as one of the seven pillars underpinning the aging process [9] and shared by the all-major age-related diseases [4]. Moreover, the involvement of the immune system in neurodegenerative diseases has become obvious over the past few decades as reported by the activated microglia and astrocytes in patients’ brains. In

2007, it was proposed that inflammaging was an example of remodeling where the increased activation of with age of pro-inflammatory pathways stimulates the adaptive activation of anti- inflammatory networks [10].

An example of the complex regulation between pro- and anti-inflammatory pathways/products is represented by centenarians, who have largely escaped or postponed the major age-related diseases. These individuals are apparently capable of achieving an optimal balance between pro- and anti-inflammatory mechanisms, which likely allowed them to reach the extreme limit of human lifespan. Studies on centenarians have revealed augmented plasma levels of inflammatory molecules such as interleukin (IL)-6, interleukin (IL)-18, interleukin (IL)- 15, C reactive protein (CRP), serum-amyloid A, fibrinogen, Von Willebrand factor, resistin and leukotrienes [10-12]. However, this was counterbalanced by a concomitant large quantity of anti- inflammatory molecules (i.e. adiponectin, Transforming Growth Factor (TGF)-b1, interleukin (IL)-1 receptor antagonist (IL-1RA), cortisol, anti-inflammatory arachidonic acid compounds, such as HETE and EET) [13-17] for a detailed review on inflammaging and longevity please refer to Monti et al., [18].

Preclinical and clinical studies reported a link between neurodegenerative diseases, neuroinflammation and activation of immune system [19]. The common neuroinflammatory aspects in PD are represented by their reactive astrocytes and activated microglia~~;~~, involvement of the adaptive immune system, over expression of immune molecules such as chemokines and cytokines and increased oxygen and nitrogen reactive species concentration (ROS/RNS). Important cellular players in this scenario are glial cells, as microglia and astroglia ~~that~~ are considered a common denominator in both patients and animal models of PD.

Brain-immune cells response: Microglia

Microglia represent~~s~~ the resident immune cells in the brain, accounting for about 20% of total glial cells that derive from a myeloid-lineage progenitor in the yolk sac [20]. As CNS-resident macrophages, microglia are classified as the first line of immune response defense to CNS insults

and/or pathological conditions. After CNS damage, microglia switch from a surveillant to a reactive state, displaying changes in cell morphology and adopting an insult dependent phenotype. In the healthy brain, microglia showed small cell body morphology with several thin and long processes, although discrepancies in morphology have been described between brain area [21]. Reactive microglia suffer cytoskeletal rearrangement acquiring an ameboid shape accompained by shorter processes and larger cell bodies. Furthermore, activation of microglia through pattern recognition receptors, such as Toll-like receptors (TLRs), stimulates the synthesis of different chemokines, cytokines, inflammatory mediators and cell surface molecules, which are able to confer to microglia macrophagic and antigen-presenting cell functions. Recently it was assumed that microglia engage several phenotypes depending on the nature and intensity of the noxious stimulus and functions [22]. It is recognized that the first definition of microglia as **'**activated**'** is not adequate to qualify the full range of heterogeneous functions that activated microglia may execute. When microglia is in the activated form release pro-inflammatory factors, such as the cytokines tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), interleukin-1b (IL-1b), neuronal nitric oxide synthase nNOS and inducible nitric oxide synthase (iNOS), it assumes a pro-inflammatory phenotype. Moreover, microglia adopt functions of tissue remodeling, inflammation suppression and repair due to its ability to increase anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-b (TGF-b), and markers such as peroxisome proliferator-activated receptors-c (PPARc) and mannose receptor C type 1(MRC1). As reported by recent interpretations, the microglia cells represent an integral and important part in the architecture of neuronal circuitry and also is a ~~an~~ strong player in CNS remodeling and plasticity in both physiological and pathological states [23]. The ability of microglia to enhance communication amongst neurons and astrocytes is due to the release of cytokines and chemokines; these properties give to the microglia cells the peculiarity to "speak" with several brain cells and be a cell population with a dual physiological and immune functions, in the healthy and diseased brain [24].

While, James Parkinson, clarified the clinical and pathological description of the disease in the early nineteenth century [25], later in the twentieth century several authors reported direct evidence from post-mortem analysis ofthe brain of PD patients [26]. Initial studies, based on morphological alterations and immunohistochemical staining against HLA-DR, human glycoprotein of theMHC-II group expressed on the surface of immunocompetent cells, reported an important over expression of reactive microglia in the substantia nigra of PD patients. However, ~~but~~ microglia activated cells were also detected in the hippocampus of PD patients who also presented dementia [26]. Since the first observations of reactive microglia in postmortem brain samples of PD patients, several researchers

have proposed a role of microglia in the neuropathological processes leading to the dopaminergic degeneration that occurs in this disease [27]. Elevated expression of pro-inflammatory TNF-a, cytokines IL-6, IL-1b and NOS, detected in the SN, putamen, as well as in the cerebrospinal fluid (CSF) and serum of PD patients suggest that microglia may induce a pro-inflammatory phenotype in this pathology [28]. Conversely, the presence of anti-inflammatory molecules such as TGF-b, detected in CSF of PD patients, showed that pro- and anti-inflammatory microglia may coexist at some stage of the disease, raising the possibility that multiple phenotypes may affect variable functions during disease progression. In the substantia nigra dopaminergic neurons are vulnerable to microglial mediated neurotoxicity [29]. It was demonstrated that elevated microglial activation in the substantia nigra of patients affected by PD showed an increased expression of CR3/43 and EBM11, that is considered as marker for activated microglia [30]. The activated microglia cells, espressed as MHC-II, ICAM-1 and LFA-1 positive cells, in both putamen and substantia nigra of PD patients increased with neuronal degeneration in these areas. Futhermore, the activated microglial cells persisted regardless of the presence or absence of Lewy bodies and was often associated with neuritis and damaged neurons [27]. Moreover, autopsy brain tissue obtained substantia nigra and basal ganglia of PD patients showed that α–synuclein is detected in regions of brain where microglial activation is known to be also present. Furthermore, an *in vitro* stimulation of murine microglia with aggregated and nitrated α-synuclein shift microglial morphology to an amoeboid shape and aroused dopaminergic neurotoxicity.

Astrocytes

Astrocytes cells, also named for its star-like shaped cells, are not only structural support cells, but also important cellular players in the development of neuroinflammatory processes. They represent around 20–40% of all glia cells and are the most heterogeneous group of cells. They ~~and~~ are defined as chemically excitable cells, expressing a plethora of receptors, drug transporters, and neurotransmitters that allow the detection of neuronal activity and induce second messenger signaling within these glial cells. In this respect, astrocytes can change their intracellular calcium concentration and produce calcium waves, that is, the propagation of transient increases in internal calcium concentration across connected cells [31]. Calcium waves can either promote or diminish nearby neuronal activity, being associated with modulation of synaptic strength Astrocytes cover the entire brain and offer vital trophic, active and homeostatic roles [33]. The role of astrocytes cells is closely correlated with subtype, location, developmental stage and disease condition. Both, cell body and major processes of astrocytes, are enriched with the intermediate filament protein glial fibrillary acidic protein (GFAP). Moreover,

adult astrocytes express markers as member L1, glutamine synthetase, vimentin, aldehyde dehydrogenase 1 family, brain lipid-binding protein [33], and calcium binding protein (S100**b**). The prevalent functions of astrocyte~~s~~ cells affect control of water distribution, metabolic control of neuron-glia vascular integrity, maintenance of the blood–brain barrier (BBB) integrity, buffering ions Ca2+ and K+ ROS scavenging, trophic factor~~s~~ release, regulation of synaptogenesis, synapsis~~es~~ pruning, modulation of the tripartite synapse and definition of brain microarchitecture [34]. The detection of reactive astrocytes in the brain of PD patients is one of the key features of the disease [35].

Several models of brain degenerative diseases showed that astrocytes migrate to the site of injury and become reactive. The astrocytes change their properties in parallel with biochemical, morphological and functional alterations that occur during injury or disease. Astrogliosis is characterized by the hypertrophy of the main processes and by the upregulation of the intermediate filament proteins vimentin, GFAP, synemin and nestin [36]. Modifications are also correlated with astrogliosis ranging from reversible alterations in astrocyte gene expression and cell hypertrophy with preservation of tissue structure and cellular domains, to long-lasting scar formation that affects cell proliferation and rearrangement of tissue structure. Cellular and molecular mechanisms leading to astrogliosis are not completely clarified, but neuroinflammatory pathways appear to trigger a worsening of astrogliosis. Moreover, the activation of astrocytes is highly correlated with events triggering it and the consequences may have beneficial and detrimental effects on surrounding neural and non-neural cells [37]. In the brain, the number of dead DA neurons was inversely proportional with the number of GFAP-positive astrocytes. The analysis of GFAP density or morphology in PD patients brain indicates either no changes or mild to strong increase [38].

Recently emerging data reveal a prominent role of astrocytes in the regulation of neuroinflammationin PD [39]. In the field of beneficial effects, experiments conducted in primary cell cultures reported that astrocytes are important for both protection and survival of DA neurons [40]. Moreover, astrocytes provide neuroprotection to DA neurons either through the removal of toxic molecules from the extracellular space or through the release of antioxidant molecules and trophic factors [41]. Zhang & Barres [42] reported that inflammatory responses in microglia are amplified by astrocytes. Glial calcium-binding protein S100b, that acts as a cytokine or damage-associated molecular pattern protein [43] represents a potential marker to determine the progression of PD. S100**b** is overexpressed in post mortem substantia nigra of patients with PD compared with control tissue and it is able to upregulate the expression of the enzyme COX-2 in microglia and iNOS in astrocytes, both neuroinflammatory markers [44]. In particular the NO produced by astrocytes can be considered as a

contributing factor to the onset and progression of neurodegeneration due to the ability to activate astrocytes and mediate the disease progression [45]. It was reported that astrocytes localized in the substantia nigra pars compacta of PD patients and MPTP-treated mice, convey high levels of iNOS [46]. This NOS isoform induces high amounts of NO and superoxide radicals, two reactive species which can either directly or indirectly facilitate neuronal death. DA neuron alteration is correlated with both expression of iNOS in astrocytes and the production of NO. Moreover, under pathological conditions expression of COX-2 in the brain can increase significantly, together with production of prostaglandin E2, which are responsible for several cytotoxic effects of inflammation. Lee and colleagues [47] reported that α-synuclein, considered as pathological marker of PD and released from neuronal cells, could be shifted and stored in astrocytes and consequently induce expression of genes linked with immune functions. Actually, the role of astrocytes in PD is still debated, with both the excessive reaction of astrocytes and the loss of the normal activity of astrocytes being suggested as possible causes of the vulnerability of the DA neurons [48]. In this context, astrocytes are cells that are able to promote or prevent neuronal damage whereby, the loss of the balance between these opposing actions, could be critical for both onset and progression of PD.

Peripheral immune cells

The phagocytic cells such as macrophages ~~are~~ constitutively express MHCII, CD11b, and CD45, which can help distinguish the microglia since it has a low expression of CD45 in the inactivated state [49].In the healthy brain, the main function is immune surveillance, antigen capture, and presentation locally and in the cervical lymph nodes. After an insult or lesion, macrophages act in phagocytosis and secretion of proinflammatory cytokines such as TNFα, IFNγ and IL-12 and chemokines such as CCL2, CCL3, enhancing chemotaxis and inflammation [50]. Moreover, peripheral macrophages and microglia secrete inflammasome components such as IL-1β, IL-18-1and caspase, that stimulate neurotoxicity neurotoxicity [51].Conversely, macrophages also regulate~~d~~ the production of anti-inflammatory and neurotrophic factors [52]. Dendritic cells (DCs) have been detected in regions lacking BBB such as the circumventricular organs, in area of postnatal neurogenesis, in the perivascular space and even forming part of the glia limitans of the BBB [53]. The main grous of DC are lymphoid and myeloid and are placed into several subpopulations due to expressed markers. Their primary functions in the CNS are immune surveillance, antigen capture, delivery to the cervical lymphonodes and antigen presentation [54]. Moreover, they have a fundamental role in inflammation by stimulating cytokine~~s~~ (IL-1β, IL-23, IL-12, TNFα, IFNγ and IL-10) production [55].When the DC recognize inflammatory molecules or

damaged tissue or auto antigens, they move to sites of inflammation and to lymphonodes to stimulate T cells and thus link the innate immune response with the adaptive immune response. Actually few data showed the involvement of the DCs in the onset of PD, but they are enrolled from the blood to the brain where they prime T cells and contributing to the neuroinflammation development. A diminished number of peripheral DCs, in particular myeloid cells, are linked with the increased severity of both cognitive and motor symptoms of the disease [56]

Lymphocytes

The lymphocyte~~s~~ cells represent a subtype~~s~~ of white blood cells in a vertebrate's immune system. They include natural killer cells (NK cells), T cells and B cells. Lymphocytes protect~~s~~ the brain from ~~a~~ an inflammatory phenomenon that could significantly compromise the homeostasis required for neural functions [57]. The cellular immune surveillance in brain of healthy human defers amongst CNS areas and the higher numbers of immune cells are situated in brain area where the tight junction barrier of the BBB is diminished, such as the circumventricular organs and the ventrorostral areas of the medulla oblongata [58] .Moreover, in the brains of healthy humans, activated central memory T cells that showed high levels of CXCR3,CCR7 and L-selectin are detected in the choroid plexus in the sub arachnoid space and also in the CSF [59].

Cytokines and chemokines

A growing body of clinical and experimental evidence has supported the role of oxidative stress and inflammatory mediators such as cytokines and chemokines, as events correlated with microglial reaction in PD patients [60]. In particular it ~~was~~ has demonstrated ~~an~~ a higher expression of the chemokine receptor CXCR4 and of its natural ligand CXCL12 in dopaminergic neurons of the substantia nigra of PD patients; this observation was also associated with an increase in microglial activation [61]. CXCL12/CXCR4 signaling can stimulate neurotoxic events such as activation of caspase-3. Cerebrospinal fluid (CSF) reflects metabolic and pathological alterations of the CNS more directly than any other body fluid; for this reason CSF represents a good source for neuroinflammation evaluation and PD biomarkers [62]. In this respect, several researchers have studied levels of inflammatory markers in the CSF of PD patients. Elevated levels expression of IL-6 and IL- 1 β were identified in the CSF of PD patients [63].Moreover, concentrations of IL-2, IL-4, IL-1 β and transforming growth factor- (TGF-α) in ventricular CSF were higher in juvenile PD patients than those reported in the controls [64]. Free TGF-α 1 and total TGF-α 2 levels were also elevated in post-mortem

ventricular CSF of PD patients in comparison with age and gender-matched controls [65]. Several scientific studies ~~data~~ supported the hypothesis that peripheral inflammatory/immune markers are correlated to inflammatory events in the onset of PD. Analyses of cytokines in serum or plasma showed elevated proinflammatory cytokines expression such as TNF-α [66] and its soluble receptors sTNFR1 [67] ands TNFR2 and IL-1β in PD patients in comparisonwith controls [68]. Moreover elevated serum levels of macrophage migration inhibitory factor (MIF) were detected in PD patients in comparison with healthy subjects. In agreement, levels expression of IL-2[69], IL-6 [70], interferon (IFN)-γ [69] and the anti-inflammatory cytokine IL-10 were found to be increased in PD patients [71]. Furthermore IL-6 plasma concentrations were ~~was~~ linked with an increased risk of developing PD. Conflicting data were reported by several researchers that did not detect~~ed~~ cytokine level~~s~~ alterations in PD. Peripheral levels of the cytokines TNF-α, IL-6, IL1-β, IFN-γ, IL-2,IL-4, IL-10 [72] and IL-12 [73] were analogous in PD patients and age- and gender-matched controls. Circulating levels of the chemokines IL-8, MIP-1α, [74], eotaxin, eotaxin-2, MCP-1 and IP-10, did not differ between PD patients and controls. These controversial findings could be explained, at least in part, by methodological differences between the studies, including heterogeneous PD samples and different techniques. Inflammation in PD patients affects also peripheral immune cells. In particular several studies reported alterations in the percentage of peripheral blood immune cells, such as lower total lymphocyte counts in comparison with controls [75]. Reduction in the number of lymphocytes may result from the decrease in the percentage of T (CD3+) and B (CD19+) cells in PD patients. Lower numbers of CD4+ cells could be demonstrated by the fact that in PD these cells showed both increased spontaneous apoptosis and activation-induced apoptosis [76]. Moreover, minimized ability of regulatory T cells (Treg) to suppress effector T cell function has been reported inPD patients [75]. Increased oxidative stress may also be linked with changes in lymphocyte profile in PD, since both whole cell and mitochondrial reactive oxygen species (ROS) in peripheral blood mononuclear cells are increased in PD [77].

Hormesis

We propose that inflammation can be considered as a type of hormetic stress, having the potential for positive outcomes at low levels (physiological inflammation) at young and adult ages, and becoming detrimental later on, in the post-reproductive period (inflammaging), especially in those people who, as a result of genetic background and/or unhealthy lifestyle, can not maintain an optimal balance between inflammaging and anti-inflammaging (unsuccessful remodelling) (Figure 1).

Strategies aimed at reducing inflammaging (systemic reduction of stress/antigenic burden, eradication of chronic infections, vaccinations and treatment with anti-inflammatory drugs) might prove effective in delaying the onset of age-related diseases. Another approach is that of reducing oxidative burden by nutritional modulation, intervention by free radical scavengers and other molecules, and hormetic strategies, which is based on the principle of stimulation of maintenance and repair pathways by repeated exposure to mild stress.

Hormesis in ageing is defined as "the life-supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress" [78]. Various stressors have been reported to have hormetic characteristics, modulating ageing and favouring longevity in cells and animals, such as heat shock, irradiation, heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, repeated physical exercise. The Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway plays a key role in modulating the hormetic stress responses. It has been recently shown that lithium, a drug approved for human use, promotes longevity and healthspan in Drosophila through the inhibition of glycogen synthase kinase-3 (GSK-3) and activation of NRF-2 [79].

The best-documented example of hormetic strategies to counteract the aging process is short- and long-term dietary/calorie restriction, including intermittent fasting [80-81]. Within the field of hormetics, all such conditions that bring about biologically beneficial effects, by initially causing low-level damage that consequently stimulates various defense pathways, are termed as *hormetins* [81]. Recently, it is been postulated that the mediterranean diet (MedDiet) exerts its healthy effects through hormetic mechanisms [82]. Specific components of the MedDiet (phytochemicals, vitamins but also lipids, carbohydrates and fibers) likely counteract the effects of inflammatory stimuli by acting as hormetins. A lifelong exposure to the MedDiet may therefore postpone the age at which the ratio pro-/anti-inflammation trespasses the threshold that separates physiological inflammation from unbalanced inflammation/inflammaging, which in turn favors age-related diseases [82]

Phytochemicals found in fruits and vegetables exhibit several neuroprotective properties. Various interventional trials suggest that a diet rich in phytochemicals may enhance neuroplasticity and resistance to neurodegeneration, postponing or preventing neurodegenerative disorders, including Alzheimer's and Parkinson's diseases in animal models [83-85]. The term "neurohormesis" indicates the ability of the central nervous system (CNS) to respond to exogenous, but also endogenous (i.e. hydrogen sulfide, nitric oxide, carbon monoxide, glutamate, Ca2+) toxic agents) [86] which represent mild stress and a driving force to augment the neuronal resistance toward stronger insults [84].

On the contrary, sedentary lifestyles often accompanied by nutrient-rich and high-fat diets may

adversely affect the brain by impairing cellular stress resistance and neuroplasticity [87]. Rats fed a diet with high levels of fat and sugar had impaired hippocampal plasticity and cognitive performance [88]. Elderly subjects with metabolic syndrome or diabetes performed worse on cognitive tests involving information processing speed, attention, and executive function compared to age-matched healthy subjects [89]. Measurements of relative levels of metabolites in human brains revealed that subjects with a high body mass index had reduced levels of N-acetyl-aspartate, an indicator of neuron metabolic health, in frontal, parietal, and temporal white matter and frontal gray matter [90].

The continuum between physiological ageing and Parkinson's Disease (PD)

Age is the major risk factor for PD, the second most frequent common neurodegenerative disease [91]. Despite this evidence, the relationship between the cellular/molecular alterations of physiological/healthy ageing and those underpinning PD pathogenesis are unclear. It can be hypothesized that PD is, at least in part, a sort of "segmental" ageing *i.e.* the result of a specific type of localized, accelerated ageing which, for reasons at present largely unknown, affects more markedly/rapidly some type of neuronal cells in the brain and other parts of the body. Indeed, even physiological ageing is characterized, among other phenomena, by a progressive decline of motor abilities and anatomo-pathological signs of neuronal degeneration in the brain, similar to those characteristics of PD, but elderly without clinical sign of PD have been detected. Data on 2500 old persons annually assessed for Parkinsonism showed that mean global Parkinsonism was 18.6%. However, the anatomo-pathological study of 744 of these subjects deceased without PD (mean age at death: 88.5 yrs.) and who donated brains showed that: i. about 1/3 of cases had mild or more severe nigral neuronal loss; ii. about 17% had Lewy bodies; iii.10% of the brains showed both nigral neuronal loss and Lewy bodies [92]. Thus, there is an apparent continuum between physiological ageing and neurodegenerative age-related motor disorders. Idiopathic PD manifests with a combination of motor and non-motor features which can precede for decades the onset of motor signs, and is thought to result from the combined effects of ageing and genetic risk factors plus lifestyle/nutritional/environmental determinants, including possible exposure to toxic substances. At present, identified PD-associated environmental and genetic risk factors are of limited clinical usefulness in the majority of PD patients.

The environmental component(s) of sporadic PD is/are unclear although many factors have been found to be associated with higher risk of PD. Increasing evidence suggests that PD be included on the growing list of diseases associated with vitamin D insufficiency and that we should routinely monitor vitamin D levels in patients with PD [93]. One of the most advanced and appealing hypotheses is that environmental stressors may contribute to age-related neuro-degeneration by favoring cell

senescence of glia, thus creating a chronically inflamed milieu in the brain [94]. From this point of view the known involvement of the bi-directional gut-brain microbiome axis in the production of a variety of neurotransmitters (serotonin, dopamine, noradrenaline, GABA, directly produced by bacteria or indirectly regulated) and in a variety of behavioural and CNS effects [95, 96]. The presence of prolonged constipation has also been associated with the possibility that inflammatory bacterial products that can travel (through retrograde transport via the vagus nerve) from the gut and reach the brain.

Recent studies showed that PD is associated to gut dysbiosis [97, 98]. The fecal concentration of short chain fatty acids (SCFA) is significally reduced in PD patients compared to controls and this reduction could impact on CNS alterations and contribute to gastrointestinal dysmobility in PD [99]. In a mouse model of PD, it has been demonstrated that gut microbiota is key player in motor deficits and microglia activation [100]. Importantly, several research findings suggest that direct modulation of gut microbiome may be applied both in treating particular age-related disorders [101], but also can be a promising therapeutic option to combat the aging process per se [102,103].

On the basis of the profound even if still unclear relationship between aging and PD, these data on PD microbiome should be interpreted within the context of the changes that occur in the gut microbiome during healthy aging. It has been recently showed that the gut microbiome undergoes profound changes with age [104, 105], which likely contribute to inflammaging and can have profound effects on the brain, owing to the increased abundance with age of bacteria involved in the tryptophan metabolism pathway, in agreement with the reduction of tryptophan (a precursor of serotonin) found in the serum of centenarians [106, 16]. Accumulating evidence shows that the age-related dysbiosis is involved in the neurological decline and promotes inflammaging [4], which play a pivotal role in both the physiological and the pathological cognitive decline [107]. While gut microbiota is able to modulate the CNS development, cognitive function and behaviour, behavioural alterations may also affect the gut microbiota composition [108]. The gut microbiota is essential for the bioavailability of substances such as polyphenols, unsatured fatty acids and anti-oxidants, which exert a protective action on cellular and neuronal aging. The gut microbiota could also contribute to the regulation of the brain function modulating the metabolism of tryptophan, an essential amino acid derived from the diet, that when metabolized from the gut is able to cross the blood-brain barrier contributing to the synthesis of the serotonin in the central nervous system [107]. These age-related changes are more evident in the amygdala, hippocampus and frontal cortex. The function of these brain areas is strongly dependent on serotonergic neurotransmission, thus involving the changes in tryptophan gut-microbiome-dependent

metabolism. Alterations in the serotonin system could represent the common denominator of the alterations of the sleep, mood and sexual conduction often observed in elderly as well as of other modifications such as diabetes and cardiovascular diseases [107].

Ageing and PD share basic propagation phenomena

The most recent data indicate that ageing and PD share basic characteristics such as accumulation of senescent cells, inflammation and propagation phenomena. Senescent cells have a secretory phenotype called SASP (Senescence Associated Secretory Phenotype) characterized by the robust expression and secretion of cytokines and other inflammatory compounds, which contribute to inflammaging [94] ("neuro-inflammaging" in the brain) [109]. Inflammaging [4,110] and cell senescence [94] can be transmitted locally to bystander cells and systemically [111] by the spill over of a variety of molecular effectors, e.g. cytokines, extracellular ATP, extracellular oligomeric complex of NLRP3 inflammasome [112], circulating mitochondrial DNA [113], circulating microRNAs [114] and shuttles (e.g. exosomes) which, on the whole, progressively impair the fitness of the organism [115].

Inflammaging appears to be causal to ageing as recently suggested by Jurk et al. [116] who showed that chronic, progressive low-grade inflammation induced in mice by knockout of the nfkb1 subunit of the transcription factor NF-κB induces an accelerated ageing which propagates to neighbour cells via ROS-mediated exacerbation of telomere dysfunction and cell senescence in the absence of any other genetic or environmental factor.

Indeed, the above-mentioned data and many others showed that there is a fundamental vicious circle where inflammaging can induce cell senescence, which in turn can produce substantial amounts of inflammatory compounds (SASP phenotype), thus propagating these two major characteristics of the ageing process, i.e. inflammation and cell senescence, locally and systemically.

The most recent literature suggests that inflammation causes DNA damage and, especially, telomere dysfunction, which is a potent activator of persistent DNA damage checkpoint activity. Pro-inflammatory signals can cause telomere dysfunction because they are closely integrated in multiple positive feedback loops with stress and nutrient signalling pathways (involving p38MAPK, TGF-b, mTOR and others) that contribute to control of mitochondrial function and ROS production. Inflammation acting chronically in vivo (inflammaging) aggravates telomere dysfunction by increasing oxidative stress [117] which then accelerates accumulation of senescent cells, which intensifies proinflammatory and pro-oxidant signalling by the SASP response and by induction of mitochondrial dysfunction, spreading DNA damage and senescence towards bystander cells Senescence-induced senescence and inflammation-induced inflammation therefore are apparently key mechanisms to

understand the ageing process and its basic propagation nature. This scenario likely represents the background fostering neurodegeneration and other age-associated diseases.

Strong evidence in favour of the propagation hypothesis of the ageing phenotype emerges from the heterochronic parabiosis experiments in rodents showing that old mice can pass blood/systemic molecules capable of accelerating the ageing of the brain of young mice (affecting in particular the ventricular neuronal stem cells) and vice versa young mice can pass blood/systemic molecules capable of rejuvenating brain cells of old mice [118-120]. A similar “rejuvenating” phenomenon can be reproduced *in vitro* using human cells (satellite muscle stem cells) [121].

Ageing and inflammaging are now thought to represent the progressive increase and spreading of inflamed micro/local- and macro/systemic-environment of aged bodies [115], fostered by: i) increased generation and exposure of cells to exogenous (e.g. alteration of gut microbiota, persistent infections such as CMV, environmental toxicants) and endogenous (e.g. increased number of senescent cells and cell debris produced by dying cells, damaged/dysfunctional mitochondria and aggregated proteins, among others) damage molecules and danger signals (collectively indicated as "garbage"); ii) a decreased garbage disposal (decreased efficiency of UPS/Proteasome, autophagy, mitophagy) and increased activation of NF-kB and inflammasomes [122-124].

Consistent with the hypothesis that inflammaging promotes age-related brain degenerative disorders in the elderly, that the NLRP3 inflammasome is likely one of the basic immune sensors that causally link systemic inflammation to aging by controlling inflammaging in both periphery and brain [123]. In individuals over 85 years of age, the elevated expression of inflammasome gene modules is associated with all-cause mortality [125]. There is a growing interest for the role of inflammasomes in the CNS (particularly regarding brain injury) [126,127]. NLRP3 activating the damage-associated molecular-patterns (DAMPs) can induce inflammatory responses in the absence of any bacterial infection or products by directly stimulating production of glial derived inflammatory mediators [128]. It has been recently shown that the neurotransmitter dopamine inhibits NLRP3 inflammasome activation [129].

Conversely, it has been reported that senescent and inflammatory cells (astrocytes) are present in the brain of PD patients [109] and a "transmission hypothesis" has been proposed regarding the pathogenesis of "PD as a prion disease" [130] where intercellular transmission of pathological protein aggregates (alfa-synuclein) occurs, causing a prion-like spreading of neuronal damage and neuro-inflammation [131,132]. Aggregated alfa-synuclein, released by neuronal degeneration, acts as an endogenous trigger inducing a strong inflammatory response in PD [133]. Similar propagation

phenomena have been described for beta-amyloid and Alzheimer's diseases [134].

Conclusions

PD could be thus properly contextualized within the ageing process based on a theoretical convergence between this recently proposed "transmission hypothesis" of neurodegenerative diseases and PD and the above-mentioned theory on the propagation of the ageing process/phenotype which emerged independently, but that altogether have a strong heuristic power. Accordingly, clinically overt PD can be considered an accelerated ageing of ~~the~~ brain, which affects specific neurons in the brain and in many other anatomical sites, owing to the co-occurrence in the same individual of a variety of genetic and non-genetic risk factors. Such a unifying perspective has the advantage of explaining the long and complex pre- clinical history of PD, which involves basic molecular dysfunction shared by and central to the ageing process, such as cell senescence, inflammation (spreading from the gut?), mitochondrial dysfunction, oxidative stress, and alteration of proteostasis and of the ubiquitin-proteasomal and autophagy systems.

The treatment of PD is still based on levodopa, fifty years after its introduction for the therapeutic management of parkinsonian patients. Levodopa is characterized by a strong symptomatic effect on motor symptoms and, at certain levels, could act following hormetic laws. For instance, the possibility to induce and to maintain the so-called “long-duration response” (135,136 Quattrone et al., 1995; Zappia et al., 1999), that is a sustained clinical benefit appearing days or weeks after beginning the treatment, is mainly due to the administration of low cumulative dosages of levodopa, whereas larger dosages may have detrimental effects (137 Zappia et al., 2000). Furthermore, it is well known that levodopa may influence complex cognitive functions, such as working memory and cognitive control, mediated by dopaminergic mesocortical pathways involving ventral tegmental area, striatum and prefrontal cortex (138 Miller and Cohen, 2001). Also for these cognitive functions, the effects of

dopaminergic drugs as levodopa could be recognized as hormetic-U-shaped dose responses, because both improvements as well as impairments could be observed. These paradoxical effects follow an inverted-U-shaped function, where both too little and too much dopaminergic activation impairs performance, depending from the initial state of the system (139 Cools and D'Esposito, 2011). Consistently, several substances/drugs used to treat PD when administered at hormetic doses are able to re-activate those mechanisms responsible for the maintenance of homeostasis. However, it is interesting to point out that these substances could have different effects at different ages and when pro-inflammatory responses tend to prevail the hormetic stimuli capable of inducing anti-inflammatory response can restore an optimal balance between pro- and anti-inflammaging (Figure 2).

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FIGURE 1

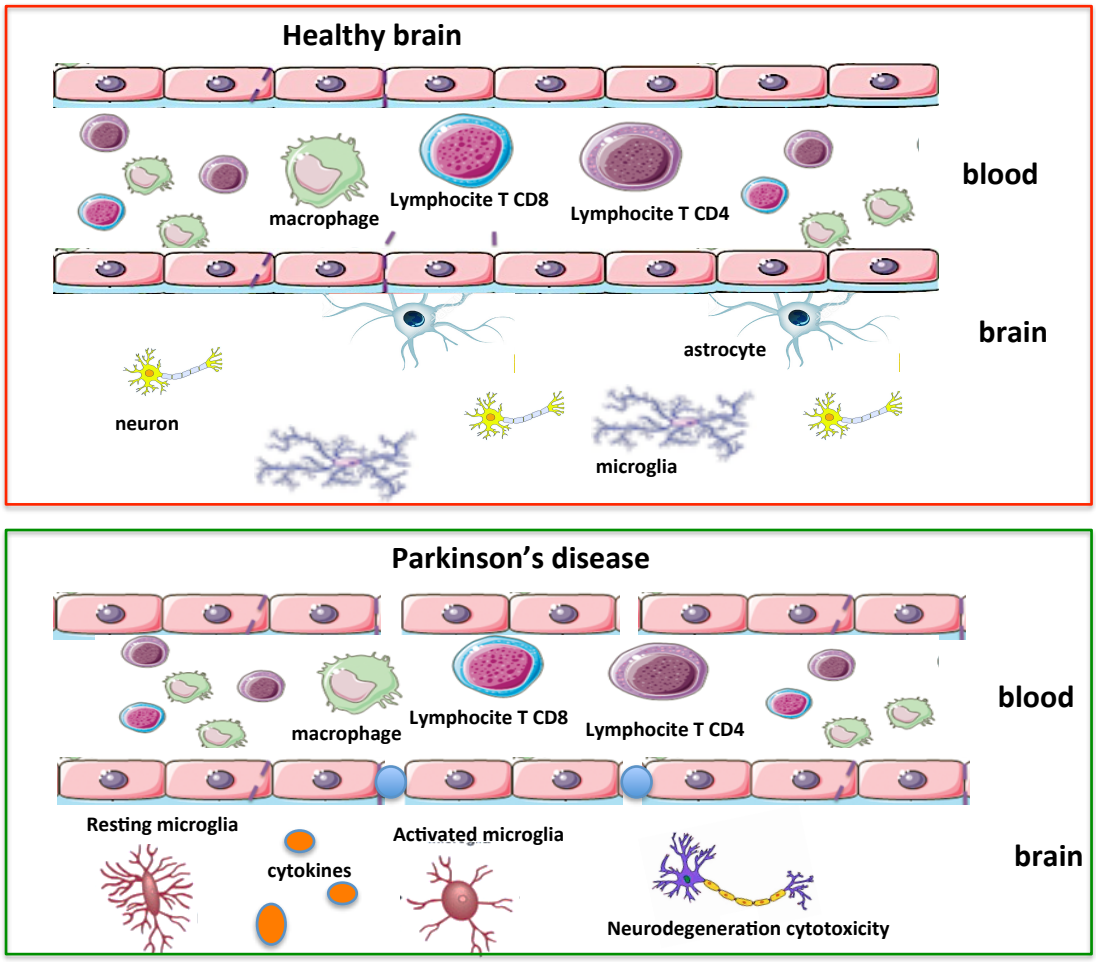

FIGURE 1: Effect of BBB breakdown in infiltration of inflammatory mediators.

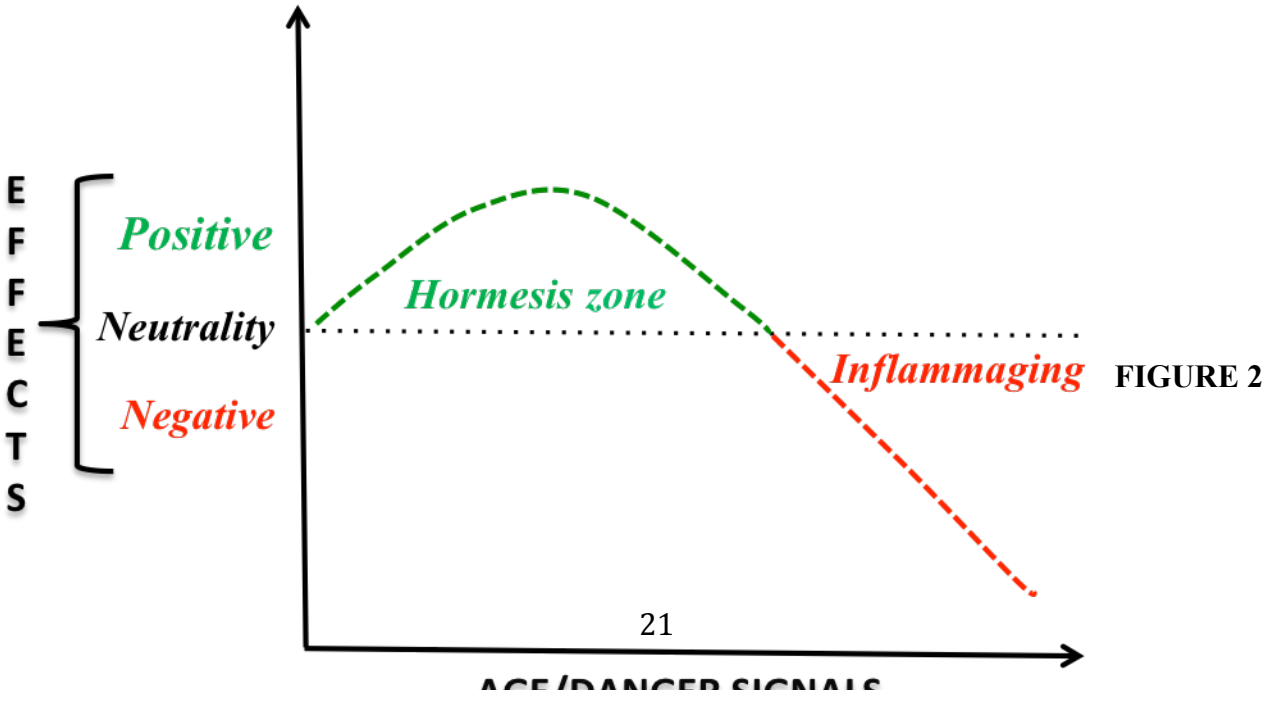

FIGURE 2

FIGURE 2: **The biphasic response of hormesis applied to inflammaging**. In the early stages of life, including the reproductive period, the production of danger signals plays a physiological role, fundamental for survival (**hormesis zone**). Later in life danger signals increase and their effect turn to be detrimental (**inflammaging**).

FIGURE 3

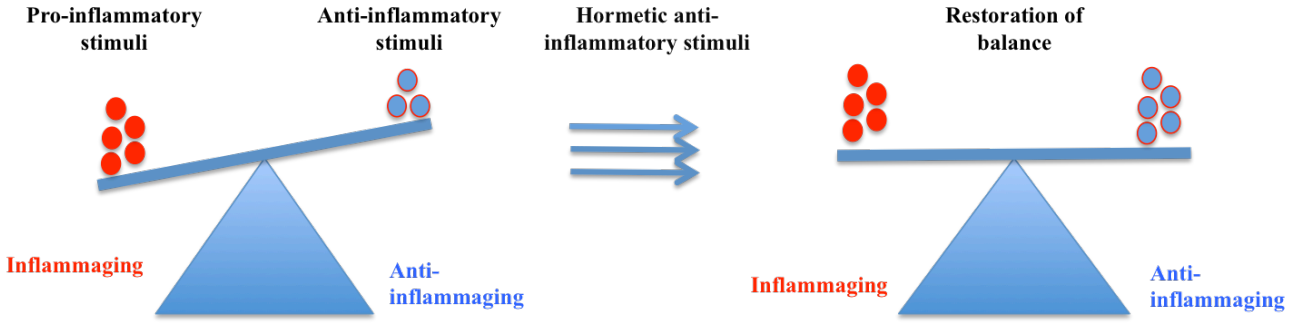

FIGURE 3: Hormetic response and the balance between inflammaging and anti-inflammaging. When pro-inflammatory responses tend to prevail hormetic stimuli capable of inducing anti-inflammatory response can help in restoring an optimal balance.

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