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Review Article

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 important to consider possible contributory factors inherent to the aging process, as age-related changes in a number of physiological systems (perhaps incurred within particular environments) appear to influence the onset and progression of neurodegenerative disorders. Accordingly, we posit that a principal mechanism underlying PD is inflammaging, i.e. the chronic inflammatory process characterized by an imbalance of pro- and anti-inflammatory mechanisms which has been recognized as operative in several age-related, and notably neurodegenerative diseases. Recent conceptualization suggests that inflammaging is part of the complex adaptive mechanisms ("re-modeling") that are ongoing through the lifespan, and which function to prevent or mitigate endogenous processes of tissue disruption and degenerative change(s). The absence of an adequate anti-inflammatory response can fuel inflammaging, which propagates on both local (i.e.- from cell to cell) and systemic levels (e.g.- via exosomes and other molecules present in the blood). In general, this scenario is compatible with the hypothesis that inflammaging represents a hormetic or hormetic-like effect, in which low levels of inflammatory stress may prompt induction of anti-inflammatory mediators and mechanisms, while sustained pro-inflammatory stress incurs higher and more durable levels of inflammatory substances, which, in turn prompt a local-to-systemic effect and more diverse inflammatory response(s). Given this perspective, new treatments of PD may be envisioned that strategically are aimed at exerting hormetic effects to sustain anti-inflammatory responses, inclusive perhaps, of modulating the inflammatory influence of the gut microbiota.

1. The continuum of physiological aging and Parkinson's Disease (PD)

Age is a major risk factor for PD, the second most frequent common neurodegenerative disease [1], affecting approximately 1% of the population over 60 years of age [2]. Despite this evidence, the relationship between the molecular/cellular processes involved in physiological/healthy aging, and those contributory to the pathogenesis of PD is still unclear. For example, it could be hypothesized that PD is, at least in part, a type of "segmental" aging, in which specific, localized, and accelerated aging mechanisms, which for reasons at present largely unknown, markedly affect dopaminergic (DA) neurons in the pars

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compacta region of the midbrain substantia nigra (SnPC). Indeed, even physiological aging is characterized by a progressive decline of motor abilities and patho-anatomic features of neuronal degeneration in the brain, which in many ways are similar to key characteristics of PD (but which do not evoke clinically-relevant signs of PD). In this light, data collected from 2500 aged persons who were annually assessed for PD revealed global Parkinsonism was 18.6%. However, post-mortem patho-anatomical studies of 744 of these subjects (who did not have PD; mean age at death: 88.5 yrs.) showed that: a) about 1/3 had mild or more severe nigral neuronal loss; b) about 17% had Lewy bodies; and c) 10% showed both nigral neuronal loss and Lewy bodies. These findings suggest that there is an apparent continuum between physiological aging and age-related neurodegenerative motor disorders. Idiopathic PD manifests a combination of motor and non-motor features that can precede the onset of clinically relevant motoric signs by decades. These prodromal motor and non-motor features are thought to result from the combined effects of aging, genetic risk factors, and particular lifestyle/nutritional/environmental determinants, inclusive of exposure to potentially toxic substances [3]. At present, environmental and genetic risk factors that are directly contributory to PD remain somewhat vague, and are of limited clinical utility in the majority of sporadic PD patients [4]).

However, we propose that lifelong exposure to (exogenous and endogenous) stressors can stimulate local and systemic adaptive responses, including activation of the immune system to incur "physiological inflammation" [5]. This inflammatory response, which can be considered as "inflammatory tone", is highly conserved in evolution, and appears to be critical for survival. Thus, it may be that a sustained systemic inflammatory state represents a particular aging phenotype, which results from exposure to chronic stressors, perdurable inflammatory responses, and/or some combination of both. This condition, conceptualized as an important example of adaptive remodeling, is now referred to as "inflammaging" [6,7]. Recently, inflammaging was recognized as one of the seven pillars underpinning the aging process [8], and influential to many (if not all) major age-related diseases including those that are neurodegenerative [7]. It has been proposed that inflammaging can be regarded as both an age-related increase in inflammation, and a concomitant adaptive activation of anti-inflammatory processes [9].

In this light, centenarians provide good example(s) of the complex regulation of pro- and anti-inflammatory pathways/products, as these individuals have largely avoided or postponed major age-related diseases, and in particular, neurodegenerative syndromes. Studies on centenarians have revealed increased plasma levels of inflammatory molecules such as interleukin IL-6, IL-18, IL- 15, C reactive protein (CRP), serum-amyloid A, fibrinogen, von Willebrand factor, resistin and leukotrienes [9–11]. However, such increased levels of pro-inflammatory mediators were also frequently accompanied by a concomitant elevation in anti- inflammatory molecules (*i.e.* adiponectin, Transforming Growth Factor (TGF)-b1, IL-1 receptor antagonist (IL-1RA), cortisol, and anti-inflammatory arachidonic acid-derived compounds, such as HETE and EET) [12–16]; for a detailed review on inflammaging and longevity, see: Monti et al. [17]. These findings suggest that those who age "well" demonstrate anti-inflammaging mechanisms (and biomarkers) that likely counteract the adverse immune response of inflammaging. Modulating this crucial balance of pro- and anti-inflammatory processes has become a major focus of new geroscientific approaches that are attempting to more successfully treat – or prevent – major age-related diseases [8].

2. Genetic risk factors, neuroinflammation, and oxidative stress in PD

PD-related pathological changes include progressive degeneration and loss of DA neurons in the SNpc, reduction in DA content in the corpus striatum, and formation of eosinophilic inclusions (i.e.- Lewy bodies) containing α-synuclein, primarily in the remaining DA neurons [18]. While such features are noteworthy, and perhaps pathognomic. At present a complete understanding of the pathogenesis of PD remains lacking.

Still, five genes that are suspected to be highly correlated to, if not "causal" for PD have been identified via observation of rare multi-generational pedigrees in which PD segregates in a Mendelian pattern. These include: (SNCA [α-synuclein], LRRK2 [leucine-rich repeat kinase 2], PARK2 [parkin], PINK1 [PTEN induced putative kinase 1], and PARK7 [DJ-1]) [19]. The involvement – and functional roles – of these genes suggest that a dysregulation of diverse cellular processes, including mitochondrial respiratory chain function, kinase signaling, and ubiquitin-mediated protein degradation, may be potentially pathogenic in PD [19].

It is important to stress that mutations in these five genes account for no more than 2% of PD in populations of European ancestry. Recent large-scale collaborative studies have now implicated common variants in two genes, SNCA and MAPT [microtubule-associated protein tau] as susceptibility factors in PD [20,21]. These latter data are particularly intriguing because common variants in MAPT also modify risk for Alzheimer's dementia (AD), progressive supranuclear palsy, and corticobasal degeneration, suggesting the possibility of a shared pathophysiological mechanism among neurodegenerative diseases. There also is emerging evidence that mutations in the glucocerebrosidase (GBA) gene may increase the risk for both PD and Lewy Body dementia [19]. Moreover, it has been shown that the presence of GBA variants can predict a more rapid progression of cognitive dysfunction and motor symptoms in patients with PD [22].

The discovery of genetic risk factors for PD sheds light on valuable information that can be used to create new experimental models, identify promising targets for therapeutic interventions, and to select subgroups of patients and at risk subjects who may be appropriate for specific clinical trials. Preclinical and clinical studies reported a link between neurodegenerative diseases, activation of the immune system and neuroinflammation [23]. These common neuroinflammatory aspects, in both animal and human models of PD, are represented by reactive astrocytes and activated microglia, involvement of the innate and adaptive immune system, over-expression of pro-inflammatory chemo- and cytokines, and increased concentrations of reactive oxygen and nitrogen species (ROS/RNS) [24].

It has been shown that the age-related increase of both peripheral inflammation and neuroinflammation contribute to the prodromal phase of PD [25]. We hypothesize that peripheral and/or central inflammatory stimuli, affecting the brain, could induce inflammatory changes that shift microglial function toward neurodegeneration, are inductive for, and operative in PD, and thereby lead to PD signs, symptoms and progression. Data reveal that peripheral immune system activation exacerbates inflammatory responses in the brain, and may incur or increase neurodegenerative processes. However, it is unclear if the mechanisms involved in peripheral inflammation are directly or indirectly influential to – and/or involved in – those in the CNS [26].

Activation of microglial cells is, on the one hand, beneficial for neuronal tissue, as it stimulates clearance of cell debris and prompts secretion of several neurotrophic factors. But on the other, microglial inflammatory mediators modulate immune cells, act on neurons, and have been shown to contribute to neurodegenerative effects [27]. Thus, while activation of inflammatory responses is fundamental for tissue functioning and homeostasis, it can also contribute to neuronal insult. Until quite recently, the brain was considered to be an immunologically privileged organ due to the presence of the blood-brain barrier (BBB), the low expression of major histocompatibility complex class II (MHCII) proteins, and the apparent lack of cerebral lymphatic vessels.

Currently, however, this view has changed [24,28]. Louveau and colleagues have demonstrated the presence of lymphatic vessels in mouse brain [28], which could support the possibility of bi-directional peripheral-CNS entry and exit of immune cells; these findings have

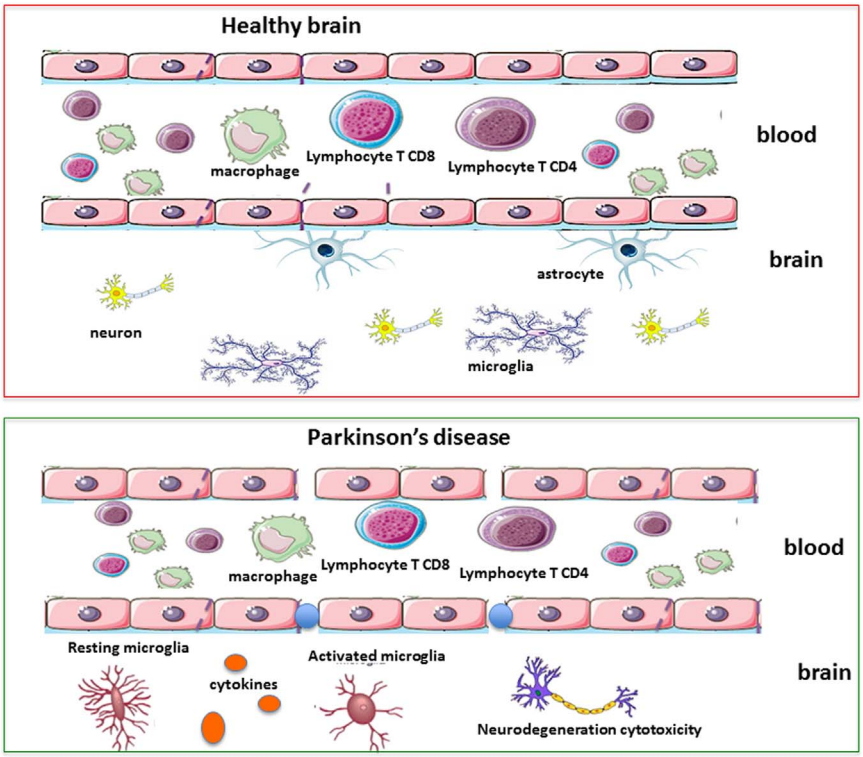

Fig. 1. Effect of BBB breakdown in infiltration of inflammatory mediators.

implications for neurodegeneration. Indeed, several neurodegenerative diseases evidence an infiltration of inflammatory and immune mediators from the periphery to the CNS [24].

Yet, while findings of brain lymphatics are compelling, the role – and dysfunction – of the BBB must stull be considered. A number of CNS pathologies, inclusive of neurodegenerative diseases incur increased BBB permeability and dysfunction (Fig. 1), and this loss of a protective barrier allows relatively free entry of circulating blood macromolecules into the CNS. Therefore, we posit that direct lymphatic access and/or compromised BBB function enable immunologically active cells and mediators to access and affect the brain, which if and when chronic, may be contributory to both inflammaging and particular neurodegenerative changes and diseases, including PD.

Additionally, changes in cerebral metabolism, either as an early-stage effect, or as a consequence of neuronal insult, may be operative in neurodegeneration and PD. There is evidence of increased oxidative stress in brain tissue of patients with PD [29]. Reactive oxygen and nitrogen species (ROS and RNS, respectively) are produced mainly in mitochondria as a by-product of aerobic metabolism. The incomplete reduction of oxygen and nitrogen leads to the generation of different radical species, such as superoxide radical (O2-), hydrogen peroxide (H2O2), nitric oxide (NO) and peroxynitrite (ONOO-). ROS/RNS generated throughout the lifespan of an organism can lead to oxidative damage to proteins, membranes, and DNA, and can impair the ability of mitochondria to produce ATP and to exert metabolic functions [30]. Even allowing that the most damaged mitochondria are degraded by mitophagy, while less defective mitochondria (which produce less ATP and less superoxide) remain and are reproductive [31], it is important to note that mitophagic efficiency (viz.- to consume malfunctioning mitochondria) also declines with age, which can result in an increased proliferation of defective, and/or less functional mitochondria, which produce higher levels of superoxide. Indeed, mitochondria of older organisms are fewer in number, larger in size and less efficient, and have been shown to produce less energy and more superoxide [32].

Mitochondrial dysfunction has been strongly associated with PD [33]. It has been proposed that a cycle in which α-synuclein aggregation and mitochondrial dysfunction exacerbate each other could explain the observation of these cellular changes in degenerating neurons in PD. Important to these effects is the reduced activity of complex I of the electron transport chain [34]. It has been proposed that low levels of α-synuclein are normally present in mitochondria, but aberrant accumulation of the protein leads to mitochondrial complex I deficits and oxidative stress [35]. The peroxisome proliferator-activated receptor-γ (PPARγ) co-activator 1α (PGC1α), a mitochondrial master transcriptional regulator, is generally under-expressed in PD [36]. Activation of PGC1α results in reduced α-synuclein oligomerization and less toxicity *in vitro*, whereas PGC1α deficiency (e.g.- by genetic knockout) increases vulnerability to α-synuclein oligomers [37]. Conversely, exposure to α-synuclein oligomers reduces levels of cellular PGC1α [37]. In animal models, injection of several toxins that impair mitochondrial function replicates a number of neuropathologic features of PD [38]. When mitochondrial transcription factor A, which is essential for mitochondrial DNA expression, is selectively depleted in DA neurons of MitoPark mice, mitochondria in DA neurons of the substantia nigra develop a defective electron transport chain, leading to neuronal degeneration in adulthood [39]. Adult mice that lack one allele of *En1* — encoding for engrailed1, which enhances nuclear translation of the mitochondrial complex proteins NADH-ubiquinone oxidoreductase 75 kDa subunit (NDUFS1) and NDUFS3—replicate several pathologic markers of PD, such as perturbations of autophagy, neuroinflammation, and progressive nigral DA cell death secondary to retrograde axonal degeneration [40]. Axonal degeneration might be an upstream and early neurodegenerative event in PD. Human brain imaging studies have demonstrated changes in the striatum several years before the onset – and diagnosis – of PD signs and symptoms [41], and recent post-mortem studies suggest that nigrostriatal axon terminals are dysfunctional or have degenerated several years before the death of neuronal cell bodies in the substantia nigra [42]. An alternative explanation for such axonal degeneration is that aggregates of α-synuclein eventually impede normal axonal transport and thereby disrupt axonal flow, metabolism and function [43].

Reactive radical species may also be involved in signaling responses, which subsequently stimulate pathways related to pro-inflammatory gene expression, cell senescence, and cell death. This inflammatory

cascade is more active during aging, and has been linked to age-associated pathologies, inclusive of neurodegenerative diseases, and PD more specifically [44]. Thus, we believe that the oxidative theory of aging [45] should be complemented by, and integrated to the inflammatory theory of aging. To be sure, inflammation has a host of characteristics that can be reciprocally interactive with oxidative stress and aging. Notably, ROS can directly or indirectly activate transcription factors such as NF-kB and AP-1 that can promote inflammation [46]. It should also be noted that transcription factors such as NF-kB are equally important for antioxidant and pro-survival cellular responses. Nevertheless, whether these antioxidant responses decrease or increase with aging is still debatable, whereas the production of ROS is well-known to increase, thus influencing the redox balance toward a pro-oxidant state [44].

ROS can damage DNA and thereby elicit a DNA damage response, in particular through engagement of the ataxia telangiectasia mutated (ATM) pathway. This pathway seems to be preferentially activated by DNA double strand breaks, and has been shown to serve as a sensor of oxidative stress [47]. The DNA damage response can also induce inflammation via the production of IL-6 [48]. Cytokines can induce DNA damage in bystander cells, which in turn produce additional cytokines, thus amplifying signaling and inflammatory responses [49]. Generally, brain cells have relatively high metabolic activity and use discrete oxidative damage-repair mechanisms to remove end-products of intracellular damage [50]. But defects of the DNA repair system in brain cells could contribute to the accumulation of potentially disruptive and toxic metabolites of cellular insult, and lead to neurological dysfunction.

Initially, DNA damages accumulate with acute cellular stress conditions, in which activation of ATM, ataxia telangiectasia and Rad3 related (ATR), E2F, BRCA1 transcription factors occur. In addition, pathways that appear to have crucial roles in neurodegenerative diseases include those involving molecules such as ATM and PTEN [51], inducing G2/M arrest, which is a result of the sequential activation of ATM and Chk [52]. Alteration(s) of these molecules are frequently found in patients with neurodegenerative diseases [53].

In general, normal cells exhibit a balance of mechanisms of DNA damage and DNA repair. Oxidative stress can induce assembly of multiprotein inflammatory complexes (i.e.- inflammasomes). Nod-like receptor protein 3 (NLRP3) is the major immune sensor for cellular stress signals (e.g.- ROS, ceramides, cathepsin B). NLRP3 activation induces caspase-1-mediated maturation of precursors of cytokines IL-1β and IL-18. Recent studies have shown that the main component of the characteristic inclusions of PD, fibrillar α-synuclein, could induce IL-1β production [54]. Moreover, NLRP3 inflammasome both participates in the regulation of DA neuron survival via uncoupling protein 2 (UCP 2) [55] and also is involved in 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP)-induced loss of DA neurons [56]. Such findings suggest a correlation of NLRP3 inflammasomes and PD. Furthermore, it has been demonstrated that inhibition of the downstream pathway of the NLRP3/caspase-1/IL-1β axis can alleviate certain signs and symptoms of PD, such as the (pro-)inflammatory response, oxidative stress, synthesis of α-synuclein, promotion of the formation of Lewy bodies, and increased toxicity of excitatory amino acids, and can interfere with the neuroprotective effect of brain-derived growth factors [57] (Fig. 2).

There are a number of possible explanations for the apparent vulnerability of nigral DA neurons to metabolic and oxidative stress [58]. First, these neurons have particularly long (up to 4.5 m), unmyelinated axons, with numerous synapses, which require considerable metabolic energy to be sustained [59]. Second, they exhibit autonomous pacemaking activity, involving cytosolic calcium oscillations and calcium extrusion, both of which require expense of energy [60]. Third, increased levels of cytosolic DA and its metabolites can cause toxic oxidative stress [61]. Lastly, mitochondrial dysfunction and increased oxidative stress can lead to the depletion of lysosomes [62] and functional impairment of the lysosomal autophagy system (LAS), and it is possible, if not likely, that several of these putatively pathogenetic pathways in PD disease are concomittantly involved and interactive [58]. In contrast, DA neurons in the adjacent ventral tegmental area are relatively resilient in PD.

2.1. Neuroinflammation and inflammaging: cells and mediators involved

It is interesting to note that the majority of non-neuronal cells involved in the inflammatory response in PD (i.e.- microglia, astrocytes, macrophages, dendritic cells and lymphocytes) exhibit the capacity to incur both beneficial as well as adverse effects consequential to differing conditions and levels of stimuli to which they are durably exposed (Fig. 1). The main features and functions of these cellular components are summarized in Table 1. A brief description of the role of each cell is presented below.

2.2. Immune cells of the brain

2.2.1. Microglia

Microglia are the primary immunological cell type in the brain, and are ontogenically derived from, and function in ways similar (if not identical) to macrophages. Microglia account for approximately 20% of the total glial cell population that is derived from a myeloid-lineage progenitor in the yolk sac [63]. Microglia function as the first line of immunological response to CNS insult and/or pathological conditions. Following CNS damage, microglia change from a surveillant to a reactive state, displaying alterations in cell morphology and phenotypes that vary based upon the type and extent of (insulting) stimulus to which they are exposed and respond [64]. Observations of reactive microglia in postmortem brain samples of PD patients have led to suggestions that microglia are involved in the neuropathological changes in DA neurons that are inherent to this disease [65].

Elevated expressions of (microglially-derived and -activating) pro-inflammatory TNF-α,β, cytokines IL-6, IL-1b and pro-oxidant NOS, have been detected in the substantia nigra, putamen, and cerebrospinal fluid (CSF) and serum of PD patients [66]; this further supports a role for microglia in inducing pro-inflammatory and pro-oxidant effects. Of note as well is that the presence of anti-inflammatory molecules (e.g.- TGF-b) in CSF of PD patients suggests 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, DA neurons are vulnerable to microglially-mediated neurotoxicity [67], and elevated microglial activation in the substantia nigra was accompanied by an increased expression of CR3/43 and EBM11 in PD [68]. Moreover, post-mortem samples of the substantia nigra and basal ganglia of PD patients exhibit co-localized increases in α–synuclein and activated microglia [68]. These human post-mortem results are supported by *in vitro* studies of murine microglia, which have shown that aggregates of nitrated α-synuclein induce DA neurotoxicity [69].

2.2.2. Astrocytes

Astrocytes primarily are involved in control of water distribution, vascular integrity, maintenance of the integrity of the BBB, ionic (e.g.- calcium and potassium) buffering, ROS scavenging, trophic factor release, regulation of synaptogenesis, synaptic pruning, modulation of the tripartite synapse, and support of brain microarchitecture [70]. Astrocytes have also been shown to play a prominent role in the regulation of neuroinflammation in PD [71]. Studies of primary cell cultures reveal that astrocytes are important for both protection and survival of DA neurons [72], affording protection to DA neurons through removal of toxic molecules from the extracellular space or through the release of antioxidant molecules and trophic factors [73]. However, Zhang and Barres [74] reported that inflammatory responses in microglia are amplified by astrocytes. Astrocytes cultured from the brains of aging rats were found to stain positively for senescence-associated β-

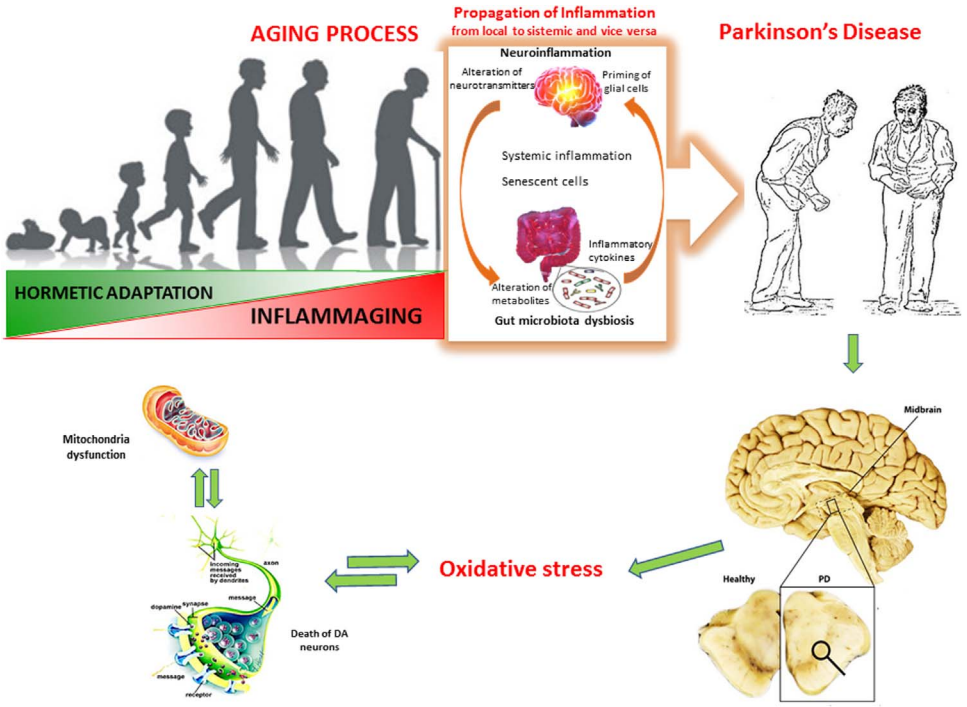

Fig. 2. Role of redox signaling and oxidative stress in PD pathogenesis and control of inflammation. Schematic representation of the connections between oxidative stress and inflammation and their modification during ageing. Aging is the major risk factor for Parkinson's Disease, and inflammaging, as a basic mechanism in neurodegeneration could be considered an a hormetic adaptation with opposite effects during the life. Senescent and inflammatory cells (astrocytes, microglia) are present in the brain of PD patients.

Table 1
Brain and peripheral immune cells favoring the PD onset and progression and involved in inflammaging and neuroinflammation.

Cell type	*Functions*	*Brain/peripheral region*	*Effects*	*References*
Activated Microglia	↑MHC-II, CR3/43, EBM11, ICAM-1, LFA-1, CXCR4/CXCL12	Substantia nigra, putament	Neurodegeneration, neuritis, neurons damage	[65, 68]
	↑TNF-α, IL-6, IL-1β ROS and NOS	Substantia nigra, Putamen and Cerebrospinal Fluid	Pro-inflammatory	[66]
	↓TGF-β	Cerebrospinal Fluid	Anti-inflammatory	[67]
	↑ α-synuclein	substantia nigra, basal ganglia	neurodegeneration	[58]
Reactive Astrocytes	Migration in injury site, ↑vimentin, GFAP, synemin and nestin	Neural and non neural cells, dopaminergic neurons	Astrogliosis, *i.e.*ipertrophy, neuroinflammation regulation	[71-73, 76-81]
	beneficial effects: release of antioxidantant trophic molecules	dopaminergic neurons, substantia nigra	progression of neurodegeneration	
	nocive effects: calcium-binding protein S100b, ↑COX-2, iNOS, NO, prostaglandinE_2 and superoxide radicals		neuronal death	
Macrophages	↑ phagocytosis, TNF-α, IFN-γ, IL-12, CCL2, CCL3; MIF	Brain lesion	Inflammation, chemotaxis Neurotoxicity	[84]
	↑inflammasome components			
	↑anti-inflammatory and trophic factors		Anti-inflammatory	[86]
Dendritic cells	IL-1β, IL-23, IL-12, TNFα, IFNγ and IL-10	Migration in brain	prime T cells and contributing to the neuroinflammation development	[91,92]
Lymphocytes including NK	Immune surveillance ↑ NK	Substantia Nigra, Blood and CSF	Peripheral inflammation and pathogen containment/clearance in neuroinflammation	[93–97]
Activated central memory Tcells	↓CD4+, CD8+, CD3+, CD19+ ↑ IL-1 b, TNF-a, sTNFR1, sTNFR2 and IL-2			

GFAP = intermediate filament protein glial fibrillary acidic protein
MIF: macrophage migration inhibitory factor

galactosidase (SA-βgal), and exhibited reduced ability to maintain the survival of co-cultured neurons [75]. *In vivo*, astrocytic glial fibrillary acidic protein (GFAP)-positive cells exhibited both a flat morphology, a characteristic of senescent cells, as well as age-related impairment in ability to sustain synaptic structure and function. These findings suggest that loss of neuroprotective effects during brain aging coincides with, and may be due, at least in part, to increased astrocytic senescence [75].

In astrocytes, glial calcium-binding protein S100b acts as a cytokine or damage-associated molecular pattern protein [76], and represents a potential marker of the progression of PD. Additionally, over-expression of S100b has been shown in post-mortem analyses of the substantia nigra of PD patients. S100b upregulates expression of inducible nitric oxide synthetase (iNOS) in astrocytes, and both S100b and iNO can induce increased activation of the pro-inflammatory enzyme cyclo-oxygenase-2 (COX-2) in microglia [77,78]. Astrocytes in the Snpc of both PD patients and MPTP-treated mice have been shown to produce high levels of iNOS [79], which induces increased formation of NO and superoxide radicals, which can directly or indirectly evoke neuronal death. Lee et al. [80] reported that α-synuclein could be transported to, and stored in astrocytes, and can induce expression of genes linked with immune functions. Therefore, both over-activation of astrocytes and the loss of normal (regulatory) astrocytic activity have been suggested as being potentially contributory to the vulnerability of DA neurons to

inflammatory and degenerative effects [81]. Indeed, it may be that astrocytes are able to prevent and/or promote neuronal damage, and a disrupted balance of these processes may be instrumental to the onset and progression of PD.

2.2.3. Peripheral immune cells

Macrophages constitutively express MHC-II, CD11b, and CD45 [82]. In the healthy brain, the main function of macrophages is immune surveillance, and antigen capture and presentation in the (cervical) lymph nodes [83]. Upon insult, macrophages act in phagocytosis and the secretion of pro-inflammatory cytokines (e.g.- TNFα, IFNγ, IL-12) and chemokines (e.g.- CCL2, CCL3), to enhance chemotaxis and induce inflammation [84]. Peripheral macrophages (and microglia) secrete inflammasome components such as IL-1β, IL-18, and caspase that stimulate neurotoxicity [85], and macrophages also produce anti-inflammatory (IL-10, TGF-β, resolvins, and ligands for TAM receptors) and neurotrophic factors (brain-derived neurotrophic factor – BDNF, nerve growth factor – NGF, and neurotrophin-3 [86].

Dendritic cells (DCs) have been detected in CNS regions lacking the BBB such as the circumventricular organs, the perivascular space, and zones of the glia limitans [87]. DCs are classified as lymphoid and myeloid, and several subpopulations have been defined with respect to the specific markers expressed [88,89]. The primary functions of DCs in the CNS are immune surveillance, antigen capture, and antigenic delivery and presentation to the cervical lymph nodes [90]. DCs play a role in inflammation by stimulating cytokine (e.g.-IL-1β, IL-23, IL-12, TNFα, IFNγ, IL-10) production [91]. When DCs recognize inflammatory molecules, damaged tissue, and/or auto-antigens, they move to sites of inflammation and to lymph nodes to stimulate T-cells, and thus link the innate and adaptive immune responses [91]. While data do not robustly suggest a direct involvement of DCs in the onset or exacerbation of PD per se, there is evidence for their capacity to prime T-cells and contribute to neuroinflammation [88]. The central migration of DCs has been implied to be operative in PD, based in part upon the finding that a diminished number of peripheral (myeloid) DCs has been correlated with the increased severity of both cognitive and motor symptoms of the disease [92].

Lymphocytes, a subtype of white blood cells in the vertebrate immune system, include natural killer cells (NK cells), T- cells and B cells. In general, a CNS role for lymphocytes is in their protection of the brain from inflammatory events that could compromise neural homeostasis [84]. A more direct role, however, has also been suggested. Both human and animal studies have demonstrated that peripheral CD4+ and CD8+ T-lymphocytes infiltrate the Snpc in PD (i.e- in human patients) and following MPTP-induced neuropathology (i.e.- in mice) [93]. This corresponds to other data that have shown that while the number of NK cells in the peripheral blood of PD patients increased, the percentage of peripheral total lymphocyte counts, and CD4+/CD8+ T-cell ratio were decreased in PD patients as compared to controls [94,95]. Such reductions in the number of lymphocytes may result from the decrease in the percentage of T (CD3+) and B (CD19+) cells in PD patients [96]; while lower numbers of CD4+ cells may be attributable to the increased spontaneous apoptosis and activation-induced apoptosis shown to occur in PD patients [96]. Moreover, minimized ability of regulatory T-cells (Treg) to suppress effector T-cell function has been reported in PD patients [94]. Increased oxidative stress may also be linked with changes in lymphocyte profile in PD, since both whole cell- and mitochondrial-ROS have been shown to be increased in peripheral (blood) mononuclear cells in PD [97].

2.2.4. Cytokines and chemokines

A growing body of evidence has supported the role of oxidative stress and inflammatory mediators, such as cytokines and chemokines, in microglial reactions in PD patients [67]. For example, a higher expression of the chemokine receptor CXCR4, and its natural ligand, CXCL12, has been demonstrated in nigral DA neurons of PD patients, and this observation was associated with an increase in microglial activation [98]. CXCL12/CXCR4 signaling can induce neurotoxic events, such as the activation of caspase-3 [99].

Cerebrospinal fluid (CSF) reflects metabolic and pathological alterations of the CNS more directly than any other body fluid, and therefore affords a viable and valuable resource for obtaining and assessing neuroinflammatory and neurodegenerative biomarkers of PD [100]. Elevated levels of IL-6 and IL-1β have been found in the CSF of PD patients [101]. Furthermore, higher concentrations of IL-2, IL-4, IL-1β and transforming growth factor-(TGF-α) were found in ventricular CSF in juvenile PD patients (vs healthy controls) [102]. Free TGF-β1 and total TGF-β2 levels were also elevated in post-mortem samples of ventricular CSF of PD patients, as compared to age- and gender-matched controls [103].

Several studies have supported the hypothesis that peripheral inflammatory/immune markers are correlated to central neuroinflammatory events in the onset of PD. Analyses of cytokines in serum or plasma showed elevated expression of pro-inflammatory cytokines, such as TNF-α [104] and its soluble receptors TNFR1 [105] and TNFR2 and IL-1β in PD patients [106]. Additionally, elevated serum levels of macrophage migration inhibitory factor (MIF) were detected in PD patients in comparison with healthy subjects [107]. Levels of IL-2 [108], IL-6 [109], interferon (IFN)-γ [108] and the anti-inflammatory cytokine IL-10 were found to be increased in PD patients [110], and increased plasma concentrations of IL-6 were correlated to an increased risk of developing PD [111]. It is important to note, however, that conflicting data exist that do not reveal alterations in cytokine levels in PD. For example, peripheral levels of the cytokines TNF-α, IL-6, IL1-β, IFN-γ, IL-2, IL-4, IL-10 [112] and IL-12 [113] were shown to be statistically similar in PD patients and age- and gender-matched controls. Circulating levels of the chemokines IL-8, MIP-1α [114], eotaxin, eotaxin-2, MCP-1 and IP-10 have also been shown not to differ between PD patients and controls [115]. These findings could be explained, to some extent, by methodological differences between the studies, inclusive of the use of heterogeneous samples of PD patients and the use of differing evaluative techniques. Still, we believe that such findings are noteworthy in that they may reveal subtle distinctions in predisposition, vulnerability and/or response to neuroinflammatory factors and processes that may be of value to assessing, treating and perhaps preventing PD, and other neurodegenerative conditions. Hence, it will be increasingly important to regard any and all such studies so as to develop an more finely-grained depiction and definition of the complex interplay between genetics, cell reactivity, inflammatory mediators, aging, and environmental factors that may regulate CNS pathology.

3. Inflammaging as a lifelong hormetic adaptation

Given the aforementioned findings, we believe – and propose - that inflammation may be regarded as a type of hormetic stress; exerting potential for positive outcomes at low levels (physiological inflammation) at young and adult ages, and becoming increasingly detrimental later, in the post-reproductive period (i.e.- inflammaging; see Fig. 2), especially in those people who, as a result of genetic background and/or unhealthy lifestyle, cannot maintain an optimal balance between inflammaging and anti-inflammaging (viz.- unsuccessful remodeling). However, the strength of hormetic processes lies in their potentially adaptive capacity throughout the lifespan. Like young and healthy middle-aged individuals, centenarians also have high levels of anti-inflammatory molecules to counteract the increased levels of inflammation that can occur with age [9–11].

Approaches aimed at reducing inflammaging (e.g.- systemic reduction of stress/antigenic burden, eradication of chronic infections, nutritional modulation, use of free radical scavenging compounds, vaccinations, and treatment with anti-inflammatory drugs) might each and all prove to be effective in delaying the onset of a number of age-related diseases. As well, these approaches may be synergized by a hormetic

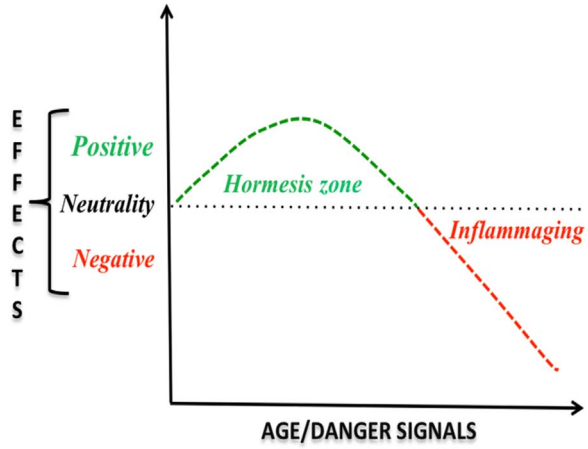

Fig. 3. The biphasic response of hormesis applied to inflammaging. In the early stages of life, including the reproductive period, the production of danger signals plays a physiological role, fundamental for survival (**hormesis zone**). Later in life danger signals increase and their effect turn to be detrimental (**inflammaging**).

strategy, which involves repeated exposure to low levels of particular stressors to induce activity of physiological mechanisms of maintenance and repair (Fig. 3). Hormesis in aging is defined as "life-supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress" [116]. Various stressors have been reported to have hormetic characteristics, including heat shock, irradiation, heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, and repeated physical exercise [116].

The nuclear erythroid 2-related factor2 (Nrf2) pathway plays a key role in mediating hormetic stress responses [117], and a decline in mitochondrial function has been reported in a variety of models of aging [32]. Therefore, maintenance of a functional mitochondrial network (via suppression of excess ROS production) may be important in reducing mitochondrial-related variables that are contributory to declining physiological function in aging. However, somewhat surprisingly, other evidence suggests that a certain level of mitochondrial impairment seems to be necessary for longevity (at least in animal models), as this activates a stress response which induces a series of cellular rescue and survival mechanisms [32]. This mild impairment can act as a hormetic signal and has been termed mitohormesis [118]. Thus, under hormetic conditions, survival advantages of low and/or very low levels of stressors are greater than potential damages [119]. One of the best-documented examples of hormetic strategies to optimize healthy aging is short-and long-term dietary/caloric restriction, inclusive of intermittent fasting [120,121]. Still, additional studies are required to more fully demonstrate this mechanism in humans, and to define the threshold at which hormetic mitochondrial impairment can become pathogenic.

Any conditions that induce biologically beneficial effects by initially causing low-level damage that consequently stimulate various adaptive mechanisms and pathways are termed *hormetins* [121]. Recently, it is been postulated that a Mediterranean diet (MedDiet) exerts healthy effects through hormetic mechanisms [122], as specific components (e.g.- phytochemicals, vitamins, lipids, particular carbohydrates and fibers) likely counteract the effects of inflammatory stimuli by acting as hormetins. Longitudinal exposure to the MedDiet may incur both a leftward shift and decreased amplitude of pro-inflammatory processes, thereby facilitating physiological inflammation and suppressing unbalanced inflammation/inflammaging that has been implied (or demonstrated) in a number of age-related diseases [122]. Animal studies suggest that a diet rich in phytochemicals may enhance neuroplasticity and resistance to neuroinflammation, mitigating or preventing neurodegenerative changes in brain that are typical in a number of age-related CNS disorders (including PD) [123–125]. Such effects may occur through a process of "neurohormesis" in which cellular components of the CNS respond to exogenous and endogenous toxic agents (e.g. H2S, NO, CO, glutamate, calcium)[126] that act as mild stressors to facilitate neuronal resistance against stronger insult(s) [124].

In contrast, sedentary lifestyle, accompanied by nutrient-rich and high-fat diets may adversely affect the brain by impairing cellular stress resistance and neuroplasticity [127]. Rats fed a diet of high levels of fat and sugar had impaired hippocampal plasticity and cognitive performance [128]. Elderly human subjects with metabolic syndrome or diabetes performed more poorly on cognitive tests involving information processing speed, attention, and executive function as compared to age-matched healthy controls [129]. Studies of human brain metabolites revealed that subjects with a high body mass index (BMI) had reduced levels of N-acetyl-aspartate (an indicator of neuronal metabolic health), in frontal, parietal, and temporal white matter, and frontal gray matter [130].

3.1. Gut microbiota, the gut-brain axis and PD: roles of tryptophan, serotonin and the kynurenine pathway

One of the most advanced and appealing hypotheses of age-related neurodegeneration posits that environmental stressors may contribute to senescence of glia, thus creating a chronically pro-inflammatory milieu in the brain [20]. It is likely that environmental and dietary factors induce peripheral changes that affect CNS function, and it is interesting to speculate if and how the recognized bi-directional gut-brain axis (and gut microbiota) may be involved in a variety of CNS effects and disorders [21,131]. Recent studies have shown that PD is associated with gut dysbiosis [132,133]. The fecal concentration of short chain fatty acids (SCFA) is significantly reduced in PD patients as compared to healthy controls, and this could both contribute to gastrointestinal dysmobility and impact CNS alterations in PD [134]. Investigations using a murine model of PD have revealed that chemicals from the gut microbiota play a contributory role in microglial activation and the production of CNS-mediated motor deficits [135]. Findings from other studies suggest that direct modulation of the gut microbiome may be useful in treating particular age-related disorders [136], as well as facilitating healthy aging, in general [137,138].

While the gut-brain relationship remains the topic of ongoing study, extant data on PD microbiome should be interpreted within the context of the changes that occur in the gut microbiome during healthy aging. For example, it has been shown that the gut microbiome undergoes profound changes with age [139,140]. These likely contribute to inflammaging and alteration of redox status, which can exert effects on the brain through the age-related increase in bacteria involved in the tryptophan metabolism pathway; findings supported by the demonstrated reduction of tryptophan in the serum of centenarians [15,141]. As well, there is evidence that the age-related dysbiosis is involved in inflammaging, oxidative damage, apoptosis and neural dysfunction that are contributory to decreased neurological activity and capacity [7,142,143].

It is important to recognize the reciprocity of gut-brain effects: changing activity of the CNS can also modify function of the gut and gut microbiota [144]; and the integrity of the gut microbiota is essential for the bioavailability of polyphenols, unsatured fatty acids, and anti-oxidants, which exert protective actions against cellular and neuronal insult, and which can sustain healthy aging. As previously noted, the gut microbiota may also regulate brain function via modulation of tryptophan, an essential dietary amino acid, which is metabolized in the gut, and can cross the blood-brain barrier to contribute to the synthesis of serotonin (5-hydroxytryptamine; 5-HT). [143]. Age-related changes in the amygdala, hippocampus and frontal cortex, as well as cognitive and behavioral processes mediated by these brain regions have been related to alterations in 5-HT function, which may occur as a result of disrupted gut-microbiome-dependent metabolism [143].

Tryptophan is also metabolized via the kynurenine pathway (KP),

which can lead to the production of nicotinamide adenosine dinucleotide (NAD+) [21], as well as quinolic and kynurenic acids. These latter compounds are neuroactive metabolites that act on N-methyl-D-aspartate (NMDA) and alpha 7 nicotinic acetylcholine receptors (nAChR) in the CNS and enteric nervous system (ENS). In the CNS, kynurenic acid has been long viewed as neuroprotective, while quinolinic acid is primarily considered an excitotoxic NMDA receptor agonist [145]. Within the gastrointestinal tract, both ligands are involved in immunoregulation [146] and kynurenic acid may have anti-inflammatory and antioxidant properties [147]. The balance between bacterial tryptophan utilization, metabolism, and synthesis, and 5-HT/kynurenine production is likely important to 5-HT transmission in both the ENS and CNS [21]. Alterations of KP have been assessed in PD (as well as other neurodegenerative diseases). PD patients have higher L-kynurenine/tryptophan ratios in serum and CSF as compared to controls, suggesting up-regulated activity of enzymes involved in catabolizing tryptophan to kynurenine (i.e.- indoleamine-2,3-di- oxygenase (IDO); tryptophan 2,3-dioxygenase (TDO)). Levels of 3-hydroxykynurenine have also been found to be increased in the putamen, prefrontal cortex and Snpc in PD patients [148]. Taken together, such results suggest that KP dysfunction may be a general feature of neurodegenerative disorders, and alterations in levels of kynurenine metabolites may be contributory to the pathologic changes that are characteristic of these diseases.

4. Aging and PD share basic propagation phenomena

Recent studies indicate that aging and PD share basic characteristics, such as accumulation of senescent cells, inflammation, and propagation phenomena. Senescent cells have a secretory phenotype, senescence associated secretory phenotype (SASP), that is characterized by robust expression and secretion of cytokines and other inflammatory compounds instrumental to CNS inflammaging [20] (i.e.- "neuro-inflammaging" in the brain) [76]. Inflammaging [7,49] and cell senescence [20] can affect local bystander cells and can exert more systemic effects [149] via the broad action of a variety of molecular effectors (e.g. cytokines, extracellular ATP, extracellular oligomeric complex of NLRP3 inflammasome [150], circulating mitochondrial DNA [151], circulating microRNAs [152] and shuttles [exosomes]) that can exert deleterious effects upon the overall fitness and health of an organism [153].

Moreover, inflammaging appears to be strongly contributory to cell and organ aging [154]. Chronic, progressive low-grade inflammation, induced in mice by knockout of the nfkb1 subunit of the transcription factor NF-κB, evoked accelerated cellular aging that was shown to propagate to neighboring cells via ROS-mediated exacerbation of telomere dysfunction and cell senescence (in the absence of other genetic or environmental factors). These data have demonstrated reciprocal effects that entail inflammaging, and induced cell senescence (through redox signaling), which in turn can produce inflammatory compounds (e.g.- SASP), and thereby propagate these characteristics both locally and systemically.

Findings to date reveal that inflammation causes DNA damage through the disruption of telomere function. Specifically, chronic inflammation (inflammaging) induces telomere dysfunction by increasing oxidative stress [44]. This accelerates cell senescence, which leads to increased pro-inflammatory and pro-oxidant signaling by the SASP response, and induction of mitochondrial dysfunction, thereby propagating DNA damage and senescence to bystander cells [44]. These processes of “senescence-induced senescence” and “inflammation-induced inflammation” appear to be important mechanisms in aging and the induction and progression of neurodegeneration and other age-associated diseases.

Strong evidence in favor of the propagation hypothesis of an aging phenotype is provided by heterochronic parabiosis experiments in rodents that have shown that molecules that induce brain aging in old mice can be passed to young mice via transfusion to incur accelerated aging/degenerative effects; and molecules capable of maintaining brain functions of young mice can be passed to older mice via blood transfusion, so as to incur cerebral “rejuvenating” effects [155–157]. Similar “rejuvenating” effects can be produced *in vitro* using media from cultured human satellite muscle stem cells [158]. Aging and inflammaging are now thought to represent the progressive increase and spread of inflamed local (i.e.- micro) and systemic (i.e.- macro) environments of aged bodies [153]. These effects are evoked and sustained by: 1) endogenous and exogenous stress, 2) toxic and cellular debris factors [160]; 3) decreased clearance of intracellular debris, as a consequence of diminished efficiency of UPS/proteasome, autophagic and mitophagic processes and 4) increased activation of NF-kB and inflammasomes [159–161].

Consistent with the hypothesis that inflammaging promotes age-related neurodegenerative disorders in the elderly, is the finding that the NLRP3 inflammasome is likely one of the basic immune sensors that link systemic inflammation to aging via control of inflammaging in both the periphery and brain [160]. In individuals older than 85 years of age, the elevated expression of inflammasome gene modules is associated with all-cause mortality [162], and there is a growing interest in the role of inflammasomes in the CNS [163,164]. NLRP3 has been shown to activate damage-associated molecular patterns (DAMPs) that induce inflammatory responses by directly stimulating production of glially-derived inflammatory mediators [165]; and recent studies have demonstrated that DA inhibits NLRP3 inflammasome activation [56]. This latter finding is of interest in that reduction of DA (caused by the dysfunction and/or loss of nigral networks) may facilitate the more widespread pattern of neuroinflammation and degeneration that is seen in mid- to later stages of PD. Of course, other mechanisms have also been considered, and a "transmission hypothesis" has been proposed that regards PD as a prion disease [166], which involves intercellular transmission of pathological protein aggregates (α-synuclein), causing a prion-like spreading of neuronal damage and neuroinflammation [167,168]. Under this hypothesis, aggregated α-synuclein, released by degenerating neurons, acts as an endogenous trigger to induce a robust inflammatory response in PD [54]. Similar propagation phenomena have been postulated for beta-amyloid in Alzheimer's disease [169].

5. Conclusions

In conclusion, we posit that PD may be hypothetically viewed as aberrantly augmented mechanisms of the aging process, which involve a convergence of the proposed "transmission hypothesis" of neurodegenerative disease, and the propagation hypothesis of the aging process/phenotype. According to this view, clinical PD could be considered as an accelerated brain aging, which is due, in part, to an interaction of genetic and non-genetic risk factors. Such a unifying perspective may be advantageous when attempting to explain pre-clinical, but nonetheless relevant factors that contribute to PD, and which may also be central to the aging process (e.g.-, cell senescence, inflammation, gut and gut-microbiome dysregulation, mitochondrial dysfunction, oxidative stress, and alteration of proteostasis and the ubiquitin-proteasomal and autophagy systems) [170–178]. It is interesting to point out that pharmacological treatments for PD could have different effects at different ages, and when pro-inflammatory responses tend to prevail, the hormetic stimuli capable of inducing anti-inflammatory responses may be able to restore an optimal balance between pro- and anti-inflammaging (Figs. 3 and 4). While these conclusions are still speculative, it is hoped that findings such as those presented, reviewed and discussed in this paper will prompt, add to, and sustain ongoing research to both address possible causes, and foster new and improved treatments (and preventive approaches) for PD and other neuro-degenerative diseases.

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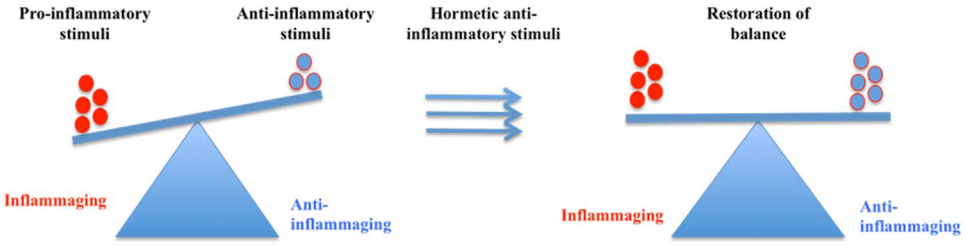

Fig. 4. Hormetic response and the balance between inflammaging and anti-inflammaging. When pro-inflammatory responses tend to prevail hormetic stimuli capable of inducing anti-inflammatory response can help in restoring an optimal balance.

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