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Review

Mitochondria and the Link Between Neuroinflammation and Neurodegeneration

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Abstract. The innate immune response is thought to exert a dichotomous role in the brain. Indeed, although molecules of the innate immune response can promote repair mechanisms, during neuroinflammatory processes many harmful mediators are also released. Signs of neuroinflammation and neurodegeneration represent a ubiquitous pathological finding during the course of several different neurological diseases. Interestingly, it has been proposed that mitochondria may exert a crucial role in the pathogenesis of both inflammatory and neurodegenerative central nervous system disorders. In this review, we describe the mechanisms by which neuroinflammation and mitochondrial impairment may synergistically trigger a vicious cycle ultimately leading to neuronal death. In particular, we describe the close relationship existing among neuroinflammation, neurodegeneration, and mitochondrial impairment in three different widely-diffused neurological diseases in which these pathogenetic events coexist, namely multiple sclerosis, Parkinson's disease, and Alzheimer's disease.

Keywords: Inflammation, mitochondria, multiple sclerosis, neurodegeneration, Parkinson's disease

INTRODUCTION

For many years the central nervous system (CNS) has been considered to be immune privileged. This view has been challenged by recent studies carried out in infectious and autoimmune models, and it is now well accepted that the nervous and immune systems are engaged in an intense cross-talk [1–5].

In particular, an active immune surveillance of the CNS occurs. Systemic inflammation and tissue damage may lead to activation of microglia, the main 'arm' of the innate CNS immune system [2,6] and to the subsequent release of inflammatory mediators and upregulation of immune receptors on other CNS cells. These events may eventually lead to tissue damage and to the release of proteins that are drained into local lymph nodes where B- and T-cell responses are initiated [2,7]. After priming, B- and T-cells cross the blood-brain barrier and migrate to the site of antigen exposure where they encounter their antigen on appropriate major histocompatibility (MHC) molecules and develop effector functions, acting synergistically in order to remove the antigenic source from the CNS through both the release of inflammatory mediators and the direct targeting of presenting cells [2].

The innate immune response is thought to exert a dichotomous role in the brain [8]. Indeed, although molecules of the innate immune response can promote repair and remyelination and trigger the production of neurotrophic factors in response to injury [8], many potentially harmful mediators such as cytokines, reactive

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oxygen species (ROS), and nitric oxide (NO) are also released [2,8].

Acute neuroinflammation usually occurs in infectious diseases, where the influx of immune cells into the CNS is aimed at removing potentially harmful pathogens and during the course of chronic autoimmune disorders of the brain, such as multiple sclerosis (MS) [9].

Besides the described conditions, in which neuroinflammation seems to represent a primary pathogenetic event, it has been demonstrated that inflammatory changes may exert a crucial role also in primarily neurodegenerative CNS disorders such as Alzheimer's disease (AD) [10] and basal ganglia disorders like Parkinson's disease (PD) [11] and Huntington's disease (HD) [12].

The close link that has been demonstrated to occur between inflammation and neurodegeneration in the pathogenesis of this heterogeneous group of neurological diseases led to the hypothesis that immune mechanisms may control and even promote neuronal degeneration and that common immunological pathways may result in neurotoxicity and subsequent neuronal death both in inflammatory and non-inflammatory CNS diseases [12,13]. For the same reasons the classical dichotomy between inflammatory and degenerative diseases of the CNS has recently been challenged and it is now believed that different neurological diseases probably share the molecular and synaptic mechanisms leading to symptoms progression and disability.

Interestingly, the similarities existing between inflammatory and neurodegenerative CNS disorders are not limited to the potential pathogenetic role of inflammatory processes. It is now well accepted that mitochondria are crucial players in the pathogenetic scenario of both inflammatory diseases, such as MS [14–16] and primary neurodegenerative disorders such as PD [17–20], AD [21,22], and HD [23].

The evidence of mitochondrial dysfunctions in both neuroinflammatory and neurodegenerative CNS disorders may lead to the hypothesis that the alteration of mitochondrial activity could somehow represent the link between neuroinflammation and neuronal degeneration.

In this review, we will describe the mechanisms by which neuroinflammation and mitochondrial impairment may synergistically trigger a vicious cycle ultimately leading to neuronal death. In particular, we will describe the close relationship existing among neuroinflammation, neurodegeneration, and mitochondrial impairment in three different widely-diffused neurological diseases in which these pathogenetic events coexist. The potential role of mitochondria as a link between neuronal inflammation and degeneration will be discussed in the context of MS, a prototypic neuroinflammatory CNS disease, and with regard to PD and AD, two primary neurodegenerative disorders.

MICROGLIA, INFLAMMATION, AND MITOCHONDRIAL IMPAIRMENT

Microglial cells, the main cell type of the innate immune system in the brain are present throughout the CNS, with the white matter generally containing fewer microglial cells than the grey matter [6].

In the adult healthy brain, the majority of microglial cells are postulated to be in the 'resting' state. Under these physiological conditions, microglial cells display a small cell soma and a characteristic ramified morphology with numerous branching processes that work as dynamic structures extending and retracting in order to monitor their microenvironment [24,25].

In response to different pathological insults and blood-brain barrier disruption, resting microglia rapidly becomes activated and reorganize its architectural structure [24,25] in order to change from a monitoring role to one of protection and repair [26].

The acute response of microglial cells to neuroinflammatory stimuli involves changes in cell phenotype and gene expression, including the *de novo* expression of the inducible isoform of nitric oxide synthase (iNOS) and cytokines such as tumor necrosis factor α (TNFα) and interleukin-1β (IL-1β). This acute microglial neuroinflammatory response involves the release of several inflammatory mediators such as cytokines and chemokines and is capable to trigger oxidative and nitrosative stress [27]. In this *scenario*, the mitochondria represent a particularly vulnerable target of oxidative and nitrosative stress and harmful proinflammatory mediators released by microglial cells.

Microglia-induced oxidative and nitrosative stress and mitochondrial impairment

Activated microglia can produce and release both ROS and nitrogen species (RNS) due to catalysis by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a multi-subunit enzyme complex that is activated during host defense [28]. Recent evidence from both neuronal and non-neuronal cells suggests that ROS and RNS function as important mes-

senger molecules that are normal components of signal transduction cascades during physiological processes. However, although during neuroinflammation the primary aim of these highly reactive free radicals is to kill surrounding pathogens, these molecules can also oxidize and damage proteins, nucleic acids, polysaccharides, and lipids and lead to mitochondrial damage. Interestingly, ROS and RNS can cause damage to essential components of the mitochondria such as mitochondrial DNA [29]. This latter evidence led to the hypothesis that ROS, generated from oxidative phosphorylation, may cause mutations in the mtDNA, which in turn leads to mitochondrial oxidative phosphorylation dysfunction and to an increased production of ROS, potentially triggering a vicious cycle [30,31]. Indeed, the mitochondrial respiratory chain, which is responsible for most of the cellular oxygen reduction and energy production, is also responsible for generating most of the cellular ROS, including superoxide (O_2), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH). Interestingly, O_2^- can interact with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), an anion with strong oxidant properties. NO is a highly reactive molecule with important physiological roles in biological systems and a key role during inflammatory processes [32]. The nitric oxide synthase (NOS) family of enzymes is responsible for the synthesis of NO, catalyzing the conversion of L-arginine to L-citrulline plus NO, and consists of three isoforms, neuronal NOS (nNOS) and endothelial NOS (eNOS) – which are constitutively expressed – and iNOS that can be induced in astrocytes or microglial cells in particular conditions, such as during inflammation [32]. The involvement of nitrosative stress in the pathogenesis of neurodegenerative and neuroinflammatory disorders is generally accepted. In these pathological conditions, NO produced in excess by the inflammation-related induction of iNOS may cause further mitochondrial impairment via different mechanisms, such as by the inhibition of cytochrome oxidase in competition with oxygen [33] and by the reversible and irreversible damage to the neuronal mitochondrial respiratory chain [34].

Microglia-released cytokines and mitochondrial function: the example of TNFα

As described above, activated microglia can also release proinflammatory cytokines such as TNF-α, a potent proinflammatory cytokine, that was isolated more than 10 years ago and that is now recognized to exert a key role as inflammatory responses modulator [35] and during the cross talk between the immune and the nervous systems [36]. Evidence to date suggests a role of this pro-inflammatory cytokine in influencing mitochondrial function. It has been shown that TNF-α affects neuritic transport of mitochondria in motor neurons, inducing mitochondrial redistribution toward the cell soma [37] and that combined treatment with TNFα and interferon-γ significantly alters morphological features and functionality of mitochondria in cells expressing mutant superoxide dismutase (mutSOD1) [38]. The same combination of cytokines (TNFα and interferon-γ), has been demonstrated to increase iNOS expression and to cause elevated NO production in primary cultures of rat oligodendrocytes associated with NO-mediated damage to mitochondrial DNA [39]. TNFα can also cause mitochondrial impairment indirectly via the autocrine stimulation of microglial glutamate release and the subsequent triggering of excitotoxic mechanisms [40]. Interestingly, it has been also demonstrated that members of the TNF family such as the TNF-related apoptosis-inducing ligand (TRAIL), might be able to interfere with the molecular mechanisms underlying the mitochondrial control of apoptosis [41] with the potential to contribute to neuronal damage during CNS inflammation [42]. In fact, mitochondria are known to provide a major switch for the initiation of apoptosis. Several death receptor-independent stimuli can trigger the translocation of pro-apoptotic molecules such as Bax to the mitochondria that in turn causes the opening of a non-specific mitochondrial inner membrane channel, the mitochondrial permeability transition pore (mtPTP), and the permeabilization of the mitochondrial outer membrane [43]. The subsequent dissipation of the mitochondrial inner membrane potential ($\Delta\Psi$m) causes the release of several molecules involved in caspase activation and in caspase-independent cell death [44]. Nevertheless, although several cytokines, including TNFα, are known to influence apoptosis in non-neuronal cells, the contribution of cytokines-induced apoptosis to neuronal death in the adult CNS still remains controversial [45].

MITOCHONDRIAL TOXINS-INDUCED NEUROINFLAMMATION

In physiological conditions mitochondria generate cellular energy in the form of ATP by the process of oxidative phosphorylation. The electron transport chain, located within the mitochondrial inner membrane, contains several components such as NADH dehydroge-

nase (respiratory complex I) and succinate dehydrogenase (respiratory complex II) and is involved in oxidative phosphorylation by oxidizing organic acids and fatty acids with atomic oxygen to generate water [46]. Mitochondrial toxins selectively targeting the respiratory complexes I and II cause oxidative phosphorylation deficits and consequently an impairment of ATP production, oxidative stress, and energy deficits that ultimately cause neuronal death [18,47]. For this reason, pharmacological inhibitors of mitochondrial respiratory complexes are currently used to induce experimental models of diseases in which mitochondria play a pathogenetic role, such as PD and HD [18, 47]. Interestingly, it has been demonstrated that mitochondrial toxins also cause different degrees of neuroinflammation, suggesting that a primary damage to the mitochondrial respiratory chain represents, *per se*, a trigger for microglial activation and neuroinflammatory processes. In particular, several different inhibitors of nicotinamide adenine dinucleotide (NADH) ubiquinone oxidoreductase (complex I), the first enzyme of the mitochondrial respiratory chain [48], have been shown to induce inflammatory reactions within the CNS. A commonly used inhibitor of mitochondrial complex I is rotenone, a naturally occurring compound derived from the roots of certain tropical plant species. Rotenone is highly lipophilic, freely crosses cellular membranes, and impairs oxidative phosphorylation by selectively inhibiting complex I [49]. In the nucleus striatum, the electrophysiological correlate of rotenone-induced neuronal dysfunction is represented by a dose-dependent and irreversible loss of the corticostriatal field potential amplitude, related to the development of a membrane depolarization/inward current in striatal spiny neurons [50]. It has been demonstrated that microglial NADPH oxidase plays an important role in mediating rotenone-induced degeneration of dopaminergic neurons [51] and that rotenone administration causes microglial activation both in rodent models [52] and in human microglial cell lines [53]. Moreover, it has been reported that nontoxic or minimally toxic concentrations of rotenone (0.5 nm) and the inflammogen lipopolysaccharide (LPS) synergistically induce neurotoxicity when the two agents are applied either simultaneously or in tandem [54].

Two other complex I inhibitors that have been widely used to model PD in animals, namely 6-hydroxydopamine (6-OHDA) and methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), have been demonstrated to induce neuroinflammatory changes in the brain. 6-OHDA, the first agent used to model PD, cannot cross the blood brain barrier and is usually administered by local stereotaxic injection directly into the substantia nigra (SN) or in the striatum in order to study the structural and electrophysiological consequences of the selective loss of the nigrostriatal pathway [55,56]. In the brains of 6-OHDA-lesioned rats, a significant increase in the number of activated microglial cells has been shown [57]. Similarly, activated microglia as well as infiltration of T-lymphocytes has been demonstrated in the brains of both monkeys and mice after systemic injection of MPTP [57–59], a protoxin that, once in the brain, is oxidized into its active metabolite, 1-methyl-4-phenylpiridinium (MPP^+) by monoamine oxidase B (MAOB). MPP^+ is taken up by the plasma-membrane dopamine transporter and is concentrated in mitochondria where it inhibits complex I causing neurotoxicity. Interestingly, microglial NADPH seems to play an important role also in MPTP-induced neurotoxicity [60].

Another mitochondrial complex inhibitor, 3-nitropropionic acid (3-NP), a suicide inhibitor of respiratory complex II, has been widely used both *in vitro* [61, 62] and *in vivo* [63,64] to model pathological changes associated with HD, a basal ganglia neurodegenerative disorder in which both mitochondrial impairment and neuroinflammation seem to play a pathogenetic role. Similarly to what it had been demonstrated for complex I inhibitors, it has been shown that 3-NP causes the activation of both a human microglia cell line and rodents microglial cells [65].

THE VICIOUS CYCLE TRIGGERED BY MITOCHONDRIAL IMPAIRMENT AND NEUROINFLAMMATION: A HYPOTHESIS

As described above, microglia are a critical point of convergence for many different pathological triggers and are able to elicit an adaptive immune response. It is believed that an acute neuroinflammatory response may be beneficial to the CNS, since it may prevent further damage to the neurons and even promote repair mechanisms [26]. In contrast, chronic neuroinflammation could represent a self-perpetuating detrimental response persisting long after the initial insult [26].

Indeed as described above, once activated, microglial cells can release potentially harmful factors, such as ROS, RNS, and proinflammatory cytokines that may stimulate the activation of additional microglial cells and cause damage to essential components of the mitochondria, such as mtDNA and enzymes of the mitochondrial respiratory chain. Conversely and at the

same time, a primary mitochondrial dysfunction, such as that triggered by the administration of mitochondrial toxins, is able to induce microglial activation. Interestingly, both these events (microglial activation and mitochondrial impairment) have been demonstrated to trigger, *per se*, the molecular pathways leading to neuronal degeneration [27,66].

For this reason, it is possible to hypothesize that, independently from the primary pathogenetic event (either inflammatory or mitochondrial in nature), the complex and probably synergistic interaction between neuroinflammatory processes and mitochondria may result in the generation of a self-renewing vicious cycle ultimately leading to neuronal death. In this context, the mitochondria may be seen as a crucial link between neuroinflammation and neurodegeneration. This latter hypothesis would explain the fact that signs of mitochondrial impairment seem to be a constant finding in both inflammatory and neurodegenerative CNS diseases and that in different human pathological conditions neurodegeneration and neuroinflammation are closely intertwined processes. The possibility of a vicious cycle triggered by either inflammation or by primary mitochondrial impairment has not been proved to date and it still represents a hypothesis that requires further experimental efforts to be demonstrated.

MITOCHONDRIA: THE ULTIMATE TARGET LEADING TO NEURODEGENERATION IN MULTIPLE SCLEROSIS?

MS is one of the most common chronic and disabling disorders of the CNS and is considered to be primarily an inflammatory disorder. MS usually begins in young adulthood and, in 80–90 % of the cases, starts with a relapsing-remitting course [9]. In the initial, relapsing-remitting phases of the disease, inflammation is usually transient. However, over the course of the disease, MS-associated pathological changes become dominated by widespread microglial activation and chronic neuroaxonal degeneration, the clinical correlate of which is progressive accumulation of disability and brain atrophy [9,67].

Accordingly, over time, the number of relapses decreases, but a high proportion of patients develop the so-called secondary progressive phase of MS, in which neurological deficits progress independently of relapses [9].

There is substantial evidence that immune dysregulation plays an important role in the disease process in MS, at least in its initial phases. In particular, the prevailing hypothesis is that autoreactive T cells of the $CD4^+$ T helper (Th)1 population orchestrate the MS inflammatory pathogenetic process [2]. According to the primary inflammatory nature of this CNS disease, MS demyelinated areas are characterized by inflammatory infiltrates that contain blood-derived myelin-specific T cells, B cells, and a multitude of non-specific, effector mononuclear cells [68], and it has been demonstrated that inflammatory cytokines (such as IL1β, TNF-α) and other inflammation-related molecules (such as iNOS) are expressed in active MS plaques [68,69].

Unfortunately, the precise mechanisms underlying neuroaxonal damage and disease progression in MS are still far from being elucidated [70]. A potential pathogenetic role of mitochondrial dysfunction in mediating the MS-related neuroaxonal damage has been proposed, based on the evidence that alterations in mitochondrial DNA, mitochondrial structural changes, and abnormal mitochondrial enzyme activities have been reported in patients with MS and in experimental models of the disease [71]. In particular, in MS motor cortex, several nuclear-encoded mitochondrial genes, and the functional activities of mitochondrial respiratory chain complexes I and III have been found to be decreased [14]. Moreover, it has been recently shown that functionally important defects of mitochondrial respiratory chain complex IV including its catalytic component (COX-I) are present in a particular subtype of active MS lesions [15].

It has also been shown that a complex IV defect is present in amyloid-β protein precursor positive injured demyelinated axons [16], suggesting a potentially crucial role of mitochondrial dysfunction in driving the process of axonal degeneration in MS. In consideration of the fact that microglia/macrophages are known to be a source of ROS and that complex IV is susceptible to ROS-mediated damage, the authors also determined the density of microglia and macrophages in active and inactive areas of chronic MS lesions and made correlations with complex IV activity [16]. Surprisingly, they found that a significant inverse correlation was present between the density of microglia/macrophages and global (axonal and glial) complex IV activity in demyelinated areas relative to normal appearing white matter, leading to the hypothesis that the complex IV defect associated with axonal injury was mediated by soluble products of innate immunity [16].

These data suggest that neuroaxonal damage in MS may be caused by the inflammation-induced myelin damage through a mitochondrial-centered mechanism.

A crucial question that still needs an answer is "how a process triggered by inflammation and myelin damage can lead to degeneration of axons and neurons and to the consequent development of the progressive forms of MS?".

It has been demonstrated that following the loss of myelin induced by the immune attack, axons undergo compensatory changes in order to restore impulse conduction, such as redistribution of Na^+ channels [72]. In physiological conditions, axonal Na^+ entry is rebalanced by removal through internodal Na^+/K^+ ATPase, which uses ATP produced by axonal mitochondria to pump Na^+ out in exchange for K^+. It has been postulated that, during MS, the redistribution of Na^+ channels along demyelinated axons may result in increased Na^+ influx during impulse transmission and increased ATP demand for operating $Na/^+K^+$ ATPase pumps [72]. The consequent increase in energy demand and reduced axonal ATP contents would induce a chronic state of virtual hypoxia in chronically demyelinated axons [73]. In response to such a state several detrimental molecular events are triggered, such as overactivation of ionotropic glutamate receptors, reversal of the Na^+/Ca^{2+} exchanger activity, activation of voltage-gated Ca^{2+} channels, increase in axonal Ca^{2+} concentrations, and activation of Ca^{2+}-dependent degradative pathways [73]. In this *scenario* of increased energy request, in which the balance of energy supply versus demand is altered, the mitochondria is thought to play a crucial role. In particular, since many of the detrimental effects primarily triggered by inflammatory demyelination seem to converge to the mitochondria it is possible to hypothesize that these subcellular organelles may eventually be irreversibly damaged. In this condition, mitochondrial activity could be also compromised by inherent defects in the electron transport chain as well as by soluble products released by microglial cells such as NO and peroxynitrite, causing further axonal metabolic impairment and thus triggering irreversible neuroaxonal degeneration.

MITOCHONDRIAL IMPAIRMENT, NEUROINFLAMMATION, AND NEURODEGENERATION IN PARKINSON'S DISEASE: WHICH COMES FIRST?

PD is a progressive neurodegenerative disorder that commonly presents with impairment of motor dexterity and evolves into a classic symptom triad of bradykinesia, rigidity, and rest tremor [74].

The pathological hallmark of PD is represented by the selective and region-specific loss of the dopaminergic, neuromelanin-containing neurons of the pars compacta of the SN [74]. However, during PD, dopaminergic neurons are not the only cells to degenerate and cell loss has also been demonstrated in the locus coeruleus, dorsal nuclei of the vagus, raphe nuclei, nucleus basalis of Meynert, and catecholaminergic brain stem structures [74]. The progressive loss of midbrain dopaminergic neurons and of their projecting fibers leads to lower levels of dopamine in the nucleus striatum and to consequent development of synaptic and neuronal network abnormalities that probably underlie symptoms onset [75,76].

The mechanisms triggering neuronal death in PD as well as the causes underlying the specific vulnerability of selected brain structures are still unknown. The current hypothesis is that PD derives from a complex interaction of genetic factors, environmental agents, and neuronal aging [77]. Preclinical and clinical evidence suggests that mitochondrial dysfunctions play an important role in PD pathogenesis. The idea of mitochondrial dysfunction as a pathogenic mechanism in PD initially emerged following the accidental exposure of drug abusers to MPTP, resulting in an acute and irreversible parkinsonian syndrome [78]. After this first description, several other reports have shown that exposure to toxins acting by inhibiting mitochondrial function is associated with the development of a parkinson-like syndrome both in human subjects [79, 80] and in experimental animals [18]. Accordingly, mitochondria have been successfully used as subcellular targets to obtain relevant experimental models of this neurodegenerative disease [81]. Further support to the hypothesis that mitochondria could potentially play a significant pathogenetic role in PD derived from the postmortem description of complex I deficiency in the SN of patients with PD [82] and from the evidence of oxidative stress and damage markers in PD brains [83]. Recently, the identification of single genes linked to heritable forms of parkinsonism heavily influenced the research on PD etiopathogenesis, which was previously largely considered nongenetic due to the high proportion of sporadic cases. Interestingly, several genes that have been associated with the development of inheritable forms of PD such as *PARKIN*, *PINK1*, and *DJ1*, have been found to be associated with the mitochondria, further supporting the potentially crucial role of these organelles in PD [17].

A potentially central role in PD pathogenesis has also been demonstrated for inflammatory processes. In-

deed, it has been repeatedly shown that in both patients and experimental models of PD, neuroinflammation is an ubiquitous finding [11]. In particular, postmortem studies have demonstrated the presence of a conspicuous glial reaction together with signs of astrocytic reaction and infiltration of cytotoxic T lymphocytes (CD8+) in the SN of PD patients [11]. In PD brains, and in particular in the SN, the presence of neuroinflammatory processes is further supported by the evidence that several inflammation-associated molecules, such as TNFα, IL-1β, and iNOS are overexpressed [11]. The results obtained in postmortem studies have been confirmed by *in vivo* studies carried out in biological fluids (serum or cerebrospinal fluid) of patients suffering from PD, demonstrating the presence of increased concentrations of proinflammatory cytokines (TNFα, IL-1β, interleukin-6) during PD [11].

According to the described evidence it seems clear that in the SN of PD patients signs of mitochondrial dysfunction and neuroinflammation coexist. However, it has not been still demonstrated which one, of these two potentially pathogenetic processes, comes first. Mitochondrial impairment, due to genetic factors and/or environmental exposure to toxins could be the primary event triggering the pathological process. In this case, it is possible to hypothesize that microglia may become chronically activated in response to primary mitochondrial impairment and/or dopaminergic neuronal death, fueling a vicious cycle of microglial activation followed by further neuronal damage [84]. Indeed, there is evidence supporting the hypothesis that activated glial cells are able to damage dopaminergic neurons [85,86]. Another hypothesis is that inflammation may be a primary factor in PD. Accordingly, it has been shown that a single systemic (i.e., not intranigral) administration of the inflammogen LPS is able to activate brain microglia and to induce delayed and progressive loss of dopaminergic neurons in the SN [87]. Finally, it is not possible to exclude that both neuroinflammation and mitochondrial impairment may simply represent incidental epiphenomena of nigral neurons degeneration or equally important factors synergistically triggering the pathological cascade.

Further preclinical and clinical research efforts seem to be required to detect the primary event(s) triggering neuronal degeneration in PD and to unravel the mechanisms that finally lead to nigral neuronal death.

ALZHEIMER'S DISEASE, MITOCHONDRIAL DYSFUNCTION, AND NEUROINFLAMMATION

AD, the most common neurodegenerative disorder worldwide, is clinically characterized by progressive cognitive decline associated with impairment in activities of daily living and progressive behavioral disturbances throughout the disease course [88]. The earliest symptoms of AD often appear as subtle short term memory impairments with deficits in remembering minor events of everyday life. As the disease progresses, both declarative and nondeclarative memory become profoundly impaired, the capacity for reasoning, abstraction, and language are progressively lost and a profound dementia develops affecting multiple cognitive and behavioral spheres [88].

AD brains show two characteristic pathological features, extracellular deposits of amyloid-β (Aβ) peptides, so-called neuritic or senile plaques, and intracellular neurofibrillary tangles of hyperphosphorylated tau [22]. According to the amyloid hypothesis, abnormal processing, and accelerated deposition of oligomeric forms of Aβ are central mechanisms underlying pathological processes in AD [22], and it has been hypothesized that an imbalance between Aβ peptides production and clearance could be the initiating factor in AD pathogenesis [22].

Interestingly, also in AD brains, immunohistochemical, biochemical, and molecular studies have demonstrated the coexistence of inflammatory processes and signs of mitochondrial impairment [22]. Evidence of an inflammatory response in AD includes changes in microglia morphology and astrogliosis (manifested by an increase in the number, size, and motility of astrocytes) surrounding the senile plaques and the presence in postmortem AD brains and in the cerebrospinal fluid and peripheral blood of AD patients of elevated levels of expression of molecules associated with immune cells activation such as the cytokines IL-1, IL-6, and TNF-α [10,12,89,90].

Microglia surrounding plaques show a positive staining for activation markers and proinflammatory mediators, including MHC class II, TNF-α, and IL-1β [10, 12,89,90]. Interestingly, it has been demonstrated that, in addition to its direct toxic effects, Aβ is able to promote neuronal dysfunction and degeneration by the activation of microglial cells and the subsequent induction of inflammatory enzymes such as iNOS and COX-2 and release of inflammatory mediators [10]. At the same time, proinflammatory cytokines and mediators

that are overexpressed in AD brains, such as TNFα, are able to promote Aβ peptide accumulation [91] potentially triggering a vicious cycle leading to enhanced inflammation and disease progression.

Extensive literature also exists supporting a role for mitochondrial dysfunction and oxidative damage in AD pathogenesis [22,92,93]. In particular, mitochondrial abnormalities have been found both in neurons and astrocytes of AD brains [92,93]. Moreover, defects in mtDNA and signs of oxidative stress are found in the brains of AD patients and in those of AD transgenic mice [92,93]. Several lines of evidence suggest that the amyloid-β protein precursor (AβPP) and Aβ are factors contributing to mitochondrial dysfunction in AD. In particular, AβPP and Aβ seem to accumulate in mitochondrial membranes, causing mitochondrial structural and functional damage [94].

In conclusion, there is increasing evidence suggesting that both inflammatory changes and mitochondrial dysfunction may also exert a significant role in aging and AD pathogenesis, and it is interesting to note that, during AD, these main pathological events seem to be strictly linked to Aβ peptide deposition in a pathogenetic 'ménage à trois'. In fact, Aβ peptides are able to cause both microglial activation and mitochondrial dysfunction, and a current hypothesis is that accumulation of misfolded proteins may result in oxidative and inflammatory damage, which in turn leads to energy failure, synaptic and neuronal dysfunction, and degeneration in AD brains [22].

CONCLUSIONS AND FUTURE PERSPECTIVES

Signs of neuroinflammation, mitochondrial impairment, and neurodegeneration seem to be all represented in the brains of patients suffering from different neurological diseases. In particular, it appears that, independently from the primary pathogenetic insult, the formation of a self-fuelling vicious cycle may represent the final event ultimately leading to disease progression in both neurodegenerative and inflammatory CNS disorders. A more accurate characterization of the mechanisms underlying the complex cross talk-between microglial cells and neurons could lead, in the future, to the development of neuroprotective pharmacological strategies aimed at interrupting the pathogenetic cascade and at limiting the progression of these disabling neurological diseases.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=420).

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