Neurodegeneration, Mitochondria, and Antibiotics

Subjects: Neurosciences

Contributor: Juan M. Suárez-Rivero , Juan López-Pérez , Inés Muela-Zarzuela , Carmen Pastor-Maldonado , Paula Cilleros-Holgado , David Gómez-Fernández , Mónica Álvarez-Córdoba , Manuel Munuera-Cabeza , Marta Talaverón-Rey , Suleva Povea-Cabello , Alejandra Suárez-Carrillo , Rocío Piñero-Pérez , Diana Reche-López , José M. Romero-Domínguez , José Antonio Sánchez-Alcázar

Neurodegenerative diseases are characterized by the progressive loss of neurons, synapses, dendrites, and myelin in the central and/or peripheral nervous system. Actual therapeutic options for patients are scarce and merely palliative. Although they affect millions of patients worldwide, the molecular mechanisms underlying these conditions remain unclear. Mitochondrial dysfunction is generally found in neurodegenerative diseases and is believed to be involved in the pathomechanisms of these disorders. Although mitochondrial-targeted treatments are limited, new research findings have unraveled the therapeutic potential of several groups of antibiotics. These drugs possess pleiotropic effects beyond their anti-microbial activity, such as anti-inflammatory or mitochondrial enhancer function. The controversial use of antibiotics as potential therapies in neurodegenerative diseases will be discussed.

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1. Introduction

Neurodegenerative diseases are generally classified according to their clinical presentation, with movement, cognitive, and behavioral disorders being the most common. Diagnosis is generally difficult given the fact that patients normally present heterogeneous clinical features. Very often, neurodegenerative diseases are diagnosed post-mortem via neuropathological evaluation at autopsy. Nevertheless, there is currently great interest among the scientific community in the identification of biomarkers or specific genetic mutations that help clinicians anticipate the onset of these diseases to either treat them when still reversible or slow down their progression [1]. This is especially relevant given the fact that the characteristic protein abnormalities linked to these diseases are present in patients long before the clinical symptoms become noticeable [2][3].

2. Iron Accumulation and Lipid Peroxidation in Neurodegenerative Diseases

Iron accumulation and lipid peroxidation in different areas of the brain have been proposed as key disease-causing factors in many neurodegenerative diseases [4]. Abnormal iron homeostasis generally leads to iron overload, which destroys proteins and lipids via Fenton reactions [5][6]. Excessive iron accumulation and lipid peroxidation are frequently accompanied by oxidative stress, mitochondrial dysfunction, increased lipofuscin granules, and autophagy dysregulation [5][7][8]. Eventually, neuronal cell death occurs by ferroptosis, a cell death process dependent on iron-mediated lipid peroxidation.

Minocycline, a second-generation semi-synthetic tetracycline, is a known metal chelator [9], which is the reason why recent studies propose it as a potential treatment for brain iron overload [10]. In mice models, brain non-heme iron and brain iron handling protein levels decreased following minocycline treatment [11]. In fact, absorption of minocycline is significantly decreased by administration with iron supplements [12] and skin hyperpigmentation, a side effect of long-term minocycline therapy, may be related to insoluble minocycline–iron chelation products [13].

3. Neuroinflammation

Neuroinflammation is an inflammatory response within the central nervous system to events that interfere with tissue homeostasis and represents a common denominator in virtually all neurological diseases [14]. Activation of microglia, the main immune effector cells of the brain, contributes to neuronal injury by the release of neurotoxic products [14]. Toll-like receptor 4 (TLR4), expressed on the surface of microglia, plays an important role in mediating lipopolysaccharide (LPS)-induced microglia activation and inflammatory responses. Furthermore, several stress conditions can damage the outer and inner mitochondrial membranes and induce the release of mitochondrial components, such as mitochondrial mtDNA or cardiolipin [15]. These mitochondrial components are recognized as danger-associated molecular patterns (DAMPs), indicating cellular damage and thus eliciting innate immune responses [16]. Detection of both bacterial components, such as LPS, and mitochondrial DAMPs are pro-inflammatory signals. Notably, expression of most of these molecules is not restricted to specialized innate immune cells, such as macrophages, microglia, dendritic cells, or neutrophils, but also occurs in a large number of non-immune cells, including neurons. Antibiotic supplementation has been shown to regulate the neuroinflammatory response reducing its side effects [17][18][19][20].

4. Alzheimer’s Disease

Alzheimer’s disease (AD) is a degenerative disease of the central nervous system with a high incidence in elderly people [21]. The main clinical manifestations are progressive memory loss, cognitive and language communication disorders, and personality changes [22]. Its main pathological features are the appearance of senile plaque (SP) and neurofibrillary tangles (NFTs) in patients’ brains. β-amyloid (Aβ) deposition and abnormally phosphorylated Tau protein deposition are the main components of SP and NFTs, respectively [23]. There is no effective treatment for AD presently available; however, Aβ is now a key established biomarker indicating the development of AD [24]. The aggregation Aβ in AD provokes mitochondrial dysfunction [25] and dynamics impairment, including mitophagy [26].

5. Parkinson's Disease

Parkinson's disease (PD) is the second most common degenerative pathology of the central nervous system and its prevalence is higher among people over 65 years old, affecting 1–3% of the population [27][28]. The disease can present a wide range of manifestations. The most recognizable one is a mild tremor that might develop into unilateral resting tremors in the upper limbs over time. However, one out of four PD patients never develops tremors [27]. Other manifestations may involve somatomotor system dysfunction, as well as non-motor symptoms such as neuropsychiatric ones, sleep disorders, or loss of concentration [27][28]. Histopathologically, the presence of neuronal cytoplasmic inclusions called Lewis Bodies (LB), depleted dopamine levels, and loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) are characteristic features of this disease [27][28]. LB are mainly formed by the aggregation of phosphorylated α-synuclein in a misfolded fibrillary stage [27][29][30]. The formation of LB induces neuronal death which affects primarily the dopaminergic neurons in the SNpc [27][31]. The release of α-synuclein to the extracellular compartment might activate microglia and lead to the release of proinflammatory cytokines such as IL-1β through the activation of the NLRP3 inflammasome, thus amplifying neuronal damage [32][33]. Moreover, mitochondrial dysfunction plays a fundamental role in PD [27][28]. Ludtmann et al. suggested that monomeric α-synuclein has a regulatory function in mitochondrial bioenergetics by improving the efficiency of ATP synthase [29][34]. Furthermore, it has been described that aggregated α-synuclein disrupts the vesicular system and, consequently, mitophagy machinery, leading to the accumulation of dysfunctional mitochondria [30][35][36]. Mitochondrial dysfunction enhances ROS production, which may facilitate α-synuclein aggregation and would activate NLRP3 inflammasome [32][37][38]. Synaptic glutamate clearance is also compromised in PD: glutamate transporter-1 (GLT-1) is downregulated in patients causing an imbalance of glutamate homeostasis and excitotoxicity [39][40]. Currently, there is no curative treatment for PD. Most pharmacological formulations are designed to reduce the aggregation of α-synuclein, neuroinflammation, and mitochondrial dysfunction [29][41]. This has led to exploring the efficacy of existing molecules with potential activity against neuroinflammation, α-synuclein aggregation, or mitochondrial dysfunction for their application in PD. In this context, doxycycline has been identified as a potential treatment for PD, since it reduces neuroinflammation and oxidative stress, and prevents the aggregation of α-synuclein in animal models of PD [42][43].

6. Huntington's Disease

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disease characterized by progressive motor, behavioral, and cognitive decline [44]. The disease results from a CAG trinucleotide repeat expansion in the huntingtin gene (HTT) on chromosome 4. Although its driver gene was discovered in 1993, the pathophysiology of this disease remains mostly unknown [45]. The huntingtin protein is widely expressed and has many functions in human neurons [46] such as intracellular protein trafficking regulation [47], protein scaffolding [48], and synaptic vesicle formation [46][49].

7. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects the neurons responsible for controlling voluntary muscle movement [50]. ALS affects approximately 4–8 out of 100.000 individuals, with a prognosis for survival of 2 to 5 years. Abundant abnormal protein aggregations have been found in the neurons of CNS in both ALS patients and animal models of ALS [51]. The ubiquitin-proteasome system [52] and the autophagosome-lysosome pathway, including mitophagy, are the most important degradation machinery to clear the aggregated proteins [53]. As seen previously, the balance between protein aggregation and degradation is involved in the pathogenesis of several neurodegenerative diseases [54]. Most ALS-associated identified genes have been functionally implicated in autophagy and/or mitophagy, specifically in the clearance of protein aggregates and/or damaged mitochondria [55]. ALS genes known to function directly in autophagy include OPTN, TBK1, and SQSTM1. Moreover, proteins encoded by the genes C9ORF72, VCP, CHMP2B, VAPB, ALS2, SOD1, and DCTN1 have all been related to vesicular trafficking and may affect autophagy either directly or indirectly [56] [57].

8. Prion Diseases

Prion diseases are fatal neurodegenerative disorders with a highly spreading nature. The infectious agent causing prion disease, known as PrP^{Sc}, is a pathogenic misfolded and aggregated form of the cellular prion protein, PrPC [58]. Following transmission to a naive host, prions seed the misfolded form of host PrPC in an autocatalytic process, leading to an exponential increase in PrP^{Sc} in the brain and the spinal cord that eventually leads to neuronal death [59]. Prions are highly stable and accumulate in the central nervous system from months to years, eventually triggering neurodegeneration and neuronal loss as well as astrocytes and microglia activation [60]. The incubation period of the disease is exceptionally variable and may last from years to weeks. Common symptoms include behavior abnormalities, motor dysfunction, cognitive impairment, and ataxia, depending on the prion type [61]. No therapy is currently available beyond palliative care.

Mitochondria of prion-infected animals show morphological and functional abnormalities in the CNS [62]. Alterations in calcium homeostasis related to mitochondria and endoplasmic reticulum dysfunction are typical in prion diseases [63]. Increased calcium concentration promotes mitochondrial membrane loss, enhanced ROS generation, and reduced ATP production, ultimately leading to cellular apoptosis [64]. Taken together these findings suggest that mitochondrial dysfunction may contribute to the neurodegeneration observed in prion diseases. Choi et al. showed that mitochondrial fusion was upregulated in whole brains from prion-infected mice, and that expression levels of mitochondrial fission protein 1 (Fis1) and mitofusin 2 (Mfn2) were elevated in the hippocampus and striatum [65]. Furthermore, the expression of the mitochondrial fission-related protein, Drp1, was significantly reduced in the hippocampus. By inhibiting mitochondrial fission, the mitochondrial network cannot be repaired, which led to a decrease in mitochondrial mass in neurons, most of which were degenerated. These abnormalities were detected in at least four different prion disease mouse models [66]. Despite cellular Drp1 protein levels being decreased in prion-infected neuronal cells both in vitro and in vivo, the levels of the mitochondrial fission protein DLP1 were increased in some prion models. This imbalance results in extensive mitochondrial fragmentation and dysfunction, as well as neuronal death and decreased synaptic plasticity [67].

9. Primary Mitochondrial Diseases

Mitochondrial diseases are a set of highly heterogeneous disorders caused by mutations in either nuclear or mitochondrial genes that primarily affect oxidative phosphorylation and ATP synthesis. These conditions are the most common group of inherited metabolic diseases and one of the most common types of neurological disorders [68][69][70]. In fact, most mitochondrial disease patients present prominent neurologic and myopathic disorders [71]. It is widely known that neurons have a high energy demand and critically depend on mitochondria to maintain synaptic transmission through the regulation of ATP and calcium levels [72]. Early onset mitochondrial diseases are severe clinical entities often caused by autosomal recessive mutations in nuclear genes (nDNA). Examples of these include Leigh syndrome, caused by mutations in the mitochondrial oxidative phosphorylation (OXPHOS) complexes and their assembly factors [73], and Alpers–Huttenlocher syndrome, due to nDNA mutations in the mtDNA polymerase gene [74]. Other high-energy demanding tissues such as the skeletal and cardiac muscles can also be affected in patients with these diseases.

Mitochondrial diseases diagnosed in adulthood affect around 1 in 4300 adults, and are mostly caused by mtDNA mutations (approx. 87% of cases) [75]. Mitochondrial syndromes caused by mtDNA mutations that affect the nervous system include Leber's hereditary optic neuropathy (LHON), myoclonic epilepsy with red-ragged fibers (MERRF), and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [76].

The activation of mitochondrial compensatory mechanisms has been associated with the regulation of mitophagy and mitochondrial biogenesis as well as with a beneficial mild induction of ROS signaling pathways. Animals presenting impaired cardiac mitophagy and a consequent accumulation of damaged ROS-overproducing mitochondria develop cardiomyopathy. It has been observed that this condition can be improved through ROS-dependent activation of mitophagy, which can act as a mitochondrial quality control mechanism to prevent vicious cycles of ROS formation and mitochondrial dysfunction [77]. Furthermore, muscle-specific knockout mice for COX15, a complex IV assembly protein, are able to express alternative oxidases (AOX) that bypass respiratory complexes III and IV, thus transferring electrons directly to oxygen. In doing so, they exhibit decreased ROS generation, PGC-1α signaling activation, and increased lifespan [78]. Livers from adult mice depleted from superoxide dismutase 2 during embryonic development display mitochondrial adaptive responses with increased mitochondrial biogenesis and antioxidant defenses and decreased ROS levels [79]. Taken together, these results show the impressive ability of mitochondria to adapt to cellular insults.

There is no proven treatment for most primary mitochondrial diseases, only palliative therapies. Triggering mitohormesis with antibiotics such as tetracyclines or their derivatives could open the door to new therapeutic perspectives for these severe pathologies.

10. Cerebral Ischemia

Cerebral ischemia (CI) and its implications are currently one of the leading causes of mortality and morbidity worldwide. Given that the brain is one of the most energy-consuming organs, disruption of the blood supply, and

thus of nutrient and oxygen availability, can result in severe neuronal damage [80]. There is increasing evidence that acute neuronal damage induced by cerebral ischemia promotes protein aggregation, suggesting a connection between the pathomechanisms of neurodegenerative diseases and stroke [81][82][83]. Thus, it seems that brain ischemia contributes to the development of Alzheimer's disease-like neurodegeneration through various mechanisms, including accumulation of amyloid protein precursor, tau protein phosphorylation, neuroinflammation, dysregulation of Alzheimer-related genes, neuronal cell death, synaptic dysfunction, white matter alterations, and brain atrophy [84][85].

11. Neuropsychiatric Diseases: Schizophrenia and Depression

This section is included since major psychiatric and neurodegenerative diseases share genetic susceptibility and pathophysiology [86]. Thus, many causal proteins and interacting proteins, and the central role of synaptic transmission, immune and mitochondrial function are processes that participate in the shared pathogenesis.

Schizophrenia is a chronic neuropsychiatric disease that affects around 1% of the world population [87]. It may present with a wide range of symptoms either classified as positive (delusion, hallucination, and paranoia) or negative (amotivation, anhedonia, avolition, asociality, and flat affect). Negative and positive symptoms are caused by different alterations in neurotransmitter functions. Positive symptoms are caused by hyperfunction in the mesolimbic dopamine pathway [88], whereas negative symptoms may include abnormal GABAα receptors, disruption of glutamatergic systems, and abnormal microglial activation [87]. Pathophysiologically, neuroinflammation plays a key role in the disease, as evidenced by the high microglial activity that has been found in these patients [89][90]. This altered function of the brain immune system has been related to the dysfunction of glutamatergic and dopaminergic neurotransmissions [91], as well as to gray matter volume loss [90]. On the other hand, energy metabolism is also altered in the brain of patients with schizophrenia. This alteration may be due to mitochondrial dysfunction increased lactate levels and acidemia found in patients' brains [92]. This alteration may also affect neurotransmission, since dopamine levels and NMDA receptor activity are highly sensitive to pH changes [92]. Furthermore, an elevated synthesis and release of dopamine in presynaptic neurons has been found, suggesting that presynaptic mitochondria are exposed to higher levels of dopamine, a complex I inhibitor. Thus, it generates a decrease in ATP synthesis without increasing oxidative stress [88][92]. Furthermore, there are alterations in the expression of genes related to energy metabolism in the brain of schizophrenia patients [92]. Although there is no cure for schizophrenia, it is usually treated with dopamine receptor antagonists [88] which control positive symptoms but have little to no effect on negative symptoms [92][93][94].

12. Conclusions

As presented across this research, the aetiology of neurodegenerative diseases is extremely complex and can be etiologically diverse. However, most of these diseases share the common feature of mitochondrial dysfunction. The application of antibiotics to treat mitochondrial insults has always been controversial for plenty and reasonable

reasons . However, not all antibiotics function in the same way or at the same dosage. Thanks to their pleiotropic effects, these drugs may open new possibilities for the treatment of neurodegenerative disease beyond their antimicrobial activity. However, more research is needed to address the potential side effects of their chronic administration such as the risk of dissemination of antibiotic-resistant pathogenic strains. For this reason, the development of antibiotics derivatives without antimicrobial activity but retaining their neuroprotective properties will be another interesting research field in the future.

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