The possible involvement of mitochondrial dysfunctions in Lewy body dementia: a systematic review

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Summary

The hallmark of dementia with Lewy bodies (DLB) is the "Lewy body", an abnormal aggregation of alpha-synuclein found in some areas of the brain. The brain is the organ/system that is most vulnerable to this oxidative damage, and reactive oxygen species can cause neurodegenerative diseases. Different models of mitochondrial deregulation have been compared in DLB. The results are consistent with the hypothesis that alpha-synuclein affects the mitochondria themselves, increasing their sensitivity or leading to cell death through protective (neurosin) and accelerating (cytochrome c) factors.
This systematic review suggests that mitochondria play an important role in neurodegeneration and a crucial role in the formation of Lewy bodies. DLB is a disease characterized by abnormal accumulation of alpha-synuclein that could result in the release of cytochrome c and subsequent activation of the apoptotic cascade.

KEY WORDS: alpha-synuclein, dementia with Lewy bodies, mitochondria, neurodegenerative diseases, Parkinson's disease, ROS.

Introduction

Dementia with Lewy bodies (DLB) is a neurodegenerative disease clinically characterized by attentional impairment, visual hallucinations, extrapyramidal features, a fluctuating course, REM-sleep disorder and neuroleptic hypersensitivity (Duda et al., 2000). DLB was designated as a diagnostic entity in 1996, in order to distinguish it from Alzheimer's disease (AD) and Parkinson's disease (PD), whose clinical features and molecular pathology are similar (Dickson et al., 1991; Aminiff et al., 2008; Dickson et al., 1994, Hansen et al., 1989). Lewy bodies (LBs) are the hallmark lesions of degenerating neurons in the brains of patients with DLB. They are located predominantly in neurons of the substantia nigra (SN) or locus coeruleus (brainstem predominant form) and/or in the cerebral cortex (transitional Lewy body disease) or limbic structure (diffuse Lewy body disease), and they lead to significant impairment of nigrostriatal dopaminergic and basocortical cholinergic neurotransmission. The three main anatomopathological patterns of DLB are described in Table I and the pathological hallmarks are set out in Table II.
The Lewy body is a cellular response consisting of an abnormal accumulation of a protein called alpha-synuclein. However, using immunohistochemistry many other proteins have been detected in DLB: ubiquitin and proteasomal components, P62/sequestosome-1, neurofilament related-proteins, tubulin-related proteins, chaperone proteins and inclusion proteins.
Alpha-synuclein is a small 140-amino-acid protein that belongs to a family of related synucleins that also includes beta-synuclein. Although the function of alpha-synuclein remains unknown, several studies (Bellani et al., 2010; Mandemakers et al., 2007; Cookson, 2005; Lee et al., 2001; Branco et al., 2010) have suggested that it plays an important role in maintaining a supply of synaptic vesicles in presynaptic ter-

Table I -Patterns of dementia with Lewy bodies.

Pure form of DLB: Lewy bodies and neurites are present in brainstem nuclei and cerebral cortical regions in the absence of other pathology.
Common form of DLB: Lewy bodies and neurites are present in brainstem nuclei and cerebral cortical regions associated with numerous beta-amyloid plaques.
AD form of DLB: Lewy bodies and neurites are present in brainstem nuclei and cerebral cortical regions, associated with neuritic plaques, senile plaques and neurofibrillary tangles.

Abbreviations: DLB=dementia with Lewy bodies; AD=Alzheimer's disease

minals. Indeed, alpha-synuclein is a natively unfolded protein mainly localized in the nucleus and in the presynaptic terminals of neurons, particularly in the distal pool of synaptic vesicles and the lipid rafts of the plasma membrane (Hashimoto and Masliah, 1999).
Alpha-synuclein modulates synaptic transmission and synaptic vesicle density, and has a potential role in neurosynaptic plasticity, playing a supportive role in the folding/refolding of soluble NSF attachment protein receptor (SNARE) proteins, critical for neurotransmitter release, vesicle recycling and synaptic integrity. Fibrillar forms of alpha-synuclein are the major structural components of LBs and play a major role in the pathogenesis of DLB, PD and multiple system atrophy (Schulz-Schaeffer, 2010; Cooper et al., 2006; Bogaerts et al., 2008; Spillantini et al., 1998; Federico et al., 2012).
The abnormal deposition of alpha-synuclein is caused by two different mutations in the *SNCA* gene, located on 4q21: the first mutation, which consists of replacement of alanine with threonine at position 53 (Ala53Thr) or with proline at position 30, results in a change in the protein building block; the second mutation, which is rarer, consists of replacement of glutamic acid with lysine at position 46 (Glu46Lys) and it causes misfolding of alpha-synuclein (resulting in an incorrect three-dimensional shape).
The aim of the present review of the scientific literature was to identify mitochondrial mechanisms potentially involved in neurodegenerative diseases, and specifically in DLB pathogenesis.

Materials and methods

In October 2014 the MEDLINE electronic database (http://www.pubmed.gov) was searched using the following terms together with their synonyms and variants: “neurodegeneration”, “Lewy body dementia”, “mitochondria” “mtDNA”, “mitochondrial neurodegeneration”.
The survey was performed examining all the articles and reviews written in English and published between January 1990 and October 2014. All articles in which mitochondrial neurodegeneration was mentioned as being implicated in the etiopathogenesis of DLB were included in the analysis (inclusion criterion). Conversely, studies dealing with AD and PD were excluded (exclusion criteria).
The reference lists of all the publications taken into consideration were also examined, to identify possible further fields of research.

Results

The purpose of this review was to identify correlations between mitochondrial dysregulations and mechanisms of neurodegeneration, particularly in DLB. Alpha-synuclein inclusions can interfere with cell functions by impairing normal cellular trafficking, disrupting cell morphology, reducing axonal transport, and trapping cellular components, such as mitochondria.
In non-human experimental studies, mice lacking alpha-synuclein have been shown to exhibit impairment of mitochondrial lipid metabolism and of the electron transport chain (Ellis and Minton, 2006), and alpha-synuclein transgenic mice to exhibit reduced complex IV activity and mitochondrial DNA damage (Ott et al., 2007). Many proteins linked with DLB are mitochondrial ones. Mitochondrial associated metabolic proteins are oxidized in alpha-synuclein transgenic mice in a selective way and drosophila parkin null mutants show mitochondrial abnormalities (Greene et al., 2003); also, parkin-deficient mice show mitochondrial deficits and impaired respiratory function (Palacino et al., 2004). DJ-1 is localized in the mitochondria and modulates responses to oxidative stress (Yang et al., 2005; Ved et al., 2005). PINK1 is a protein kinase localized in the mitochondria; mutations in the kinase domain of PINK1 are associated with mitochondrial deficits (Silvestri et al., 2005). PINK1, which interacts with and complements parkin, is required for mitochondrial function (Park et al., 2006; Clark et al., 2006). LRRK2 is a kinase located in the outer mitochondrial membrane that also interacts with parkin (Smith et al., 2005). HTRA2 is localized in mitochondria and is involved in apoptosis (Yu et al., 2001). Moreover, deficits in mitochondrial function have been identified in patients with DJ-1, parkin and PINK1 mutations.
Literature data show that there are two possible mitochondrial mechanisms involved in DLB: i) mutations of

Table II - The pathological hallmarks of dementia with Lewy bodies.

Hallmarks	Areas	Authors
Lewy bodies	substantia nigra; locus coeruleus; cerebral cortex; limbic system; autonomic nervous system	Rodríguez et al., 2008 Aminoff et al., 2008
Microvacuolation (spongiform change)	Superior and inferior temporal lobes; enthorhinal and insular cortices; amygdaloid nucleus	Hansen et al., 1989
Cortical synaptic loss	–	Mukaetova-Ladinska et al., 2006 Kramer et al., 2007
Astroglial changes	Tufted astrocytes	Rodríguez et al., 2008

alpha-synuclein causing mitochondrial damage, and ii) dysfunction of mitochondrial energy metabolism in neurons.

Mutations of alpha-synuclein can cause mitochondrial damage

Alpha-synuclein works in the cell at multiple levels: it is involved in synaptic vesicle formation (Cooper et al., 2006) and in catecholamine metabolism in dopaminergic neurons (Mosharov et al., 2006); it interacts with the microtubule network (Branco et al., 2010) and, finally, it participates in calcium homeostasis regulation (Hettiarachchi et al., 2009).

Mutations or polymorphisms in both mitochondrial DNA (mtDNA) and nuclear DNA have been implicated in causing DLB and PD, and also found in patients at risk of these conditions. Current pathogenomic theories focus on a *multifactorial model of neurodegenerative disease*, which refers to a combination of genetic and environmental exposures relevant to mitochondrial dysfunction. Researchers explain that there is a "threshold effect" for developing DLB and other neurodegenerative diseases (Mandemakers et al., 2007). Indeed, heterozygous patients need to exceed a threshold in order to show the disease.

The nuclear gene mutations are in *SNCA* (synuclein, alpha (non A4 component of amyloid precursor)), *parkin (PARK2*), *PINK1* (this gene produces a protein called PTEN-induced putative kinase 1), *DJ-1 (PARK7)*, *LRRK2* (leucine-rich repeat kinase 2) and *HtrA2* (mitochondrially-located serine protease) and, directly or indirectly, they are major contributors to mitochondrial dysfunction in DLB.

The present review focuses on the relationship between genetic data on mtDNA polymorphisms, in particular with regard to the nuclear-encoded *SNCA*, *parkin*, *PINK1*, *DJ-1*, *LRRK2* and *HTRA2* genes. We highlight the importance of these genes for mitochondrial function. Mitochondrial DNA polymorphisms and haploid types are associated with DLB risk, and mutations in mtDNA or in the *POLG* gene cause PD-like symptoms. However, it has been shown that dopaminergic neurons in the central nervous system are particularly sensitive to somatic mtDNA mutations whose accumulation, moreover, is greater in PD and DLB than in other diseases. A critical threshold, about 60% mutated mtDNA, is necessary to cause dopaminergic neuronal cell death and the remaining, non-mutated mtDNA is insufficient to allow physiological function (Mandemakers et al., 2007). The mitochondrion plays a role in apoptosis through the release of pro-apoptotic molecules from the mitochondrial intermembrane space thanks to specific, but as yet unclear, mechanisms through which alpha-synuclein aggregates injure neurons (Perry et al., 2002; Green and Kroemer, 2004).

Many studies dealing with the aggregation properties of alpha-synuclein have been reported (Bellani et al., 2010; Mandemakers et al., 2007; Schulz-Schaefer, 2010, Green and Kroemer, 2004; de Castro et al., 2011; Esteves et al., 2011; Navarro and Boveris, 2012; Cookson and van der Brug, 2008; Chandra et al., 2004), but only a few have looked at degradation of alpha-synuclein (Iwata et al., 2003; Goedert, 2001; Cullen et al., 2009; Mizushima et al., 2008).

Proteolytic degradation has been analyzed as a possible cause of DLB (Iwata et al., 2003). It was found that the serine protease neurosin (kallikrein-6) degrades alpha-synuclein and co-localizes with pathological inclusions, such as LBs and glial cytoplasmic inclusions (Cookson and van der Brug, 2008). *In vitro*, it was found that neurosin prevented alpha-synuclein polymerization by reducing the amount of monomer and also by generating fragmented alpha-synucleins that themselves inhibited the polymerization. In the presence of cellular stress, the mitochondria keep on releasing neurosin to the cytosol, causing an increase in degraded alpha-synuclein species (Tatebe et al., 2010; Iwata et al., 2003). Down-regulation of neurosin causes accumulation of alpha-synuclein (Xilouri et al., 2013).

The protective role of neurosin against aggregate formation is interesting because cytochrome c (another mitochondrial protein) stimulates alpha-synuclein aggregation and it is localized in LBs. A model thus emerges whereby chronic apoptotic stressors released from mitochondria are both protective (neurosin) and accelerating (cytochrome c) factors and are accumulated in LBs (Cookson and van der Brug, 2008).

Short chromosomal duplications or trisomies containing the *SNCA* gene, plus relatively short flanking regions on chromosome 4, were also discovered in patients with PD and DLB, indicating that a 50% increase in the expression of alpha-synuclein is sufficient to cause a disease. Mutated or excess alpha-synuclein proteins may form aggregates (Cookson and van der Brug, 2008). Alpha-synuclein filaments (10-15 nm wide) are the main component of the pathological inclusions deposited in the cell bodies or in the processes of affected cells, resulting in the formation of dystrophic neurites or large axonal swellings. The polymerization of alpha-synuclein is a process involving different steps. Initially alpha-synuclein forms relatively soluble oligomeric species. Its polymerization "is associated with a dramatic conformational change from random coiled to beta-pleated sheet"; it is suggested that alpha-synuclein "progresses from an unordered monomer through partially folded intermediates and finally elongates into mature filaments"(Waxman and Giasson, 2009). The mutant alpha-synuclein leads to the deposition of several abnormally sized oligomers and polymers, which could be toxic for the cell and could increase the leakiness of synthetic lipid vesicles through two mechanisms: i) alpha-synuclein oligomers may integrate into the membrane, resulting in the formation of pores or channel-like structures that could cause uncontrolled membrane permeability and impair vesicle transport; ii) oligomers may enhance the ability of ions to move through the membrane bilayer, without the formation of pores.

As regards catecholamine metabolism, alpha-synuclein is able to inhibit dopamine (DA) release in an activity-dependent negative regulatory manner, through alterations in exocytosis; it can modulate the activation of tyrosine hydroxylase and down-regulate vesicular monoamine transporter-2 activity.

Alpha-synuclein may also be involved in the regulation of calcium homeostasis and a mutant form can give rise to neurotoxicity through alteration of L-type calcium channels (an L-type calcium channel is a voltage-dependent calcium channel; the "L" stands for long-lasting, referring to the duration of activation). Alpha-synuclein is also involved in the regulation of microtubule dynamics and overexpression of alpha-synuclein can cause disruption of the microtubule network and impaired microtubule-dependent trafficking, causing dopaminergic neuron degeneration. The alpha-synuclein degradation pathways are not well understood. The ubiquitin-proteasome system (UPS) is probably the main alpha-synuclein degradation system. Other factors may contribute to the mechanism of abnormal fibrillization:

- transient oligomeric species formed along the fibrillization pathway may be responsible for toxicity (Volles and Lansbury, 2003);
- the level of aggregation (Filosto et al., 2007);
- the way in which oligomers are deposited (Mukaetova-Ladinska and McKeith, 2006) and the way in which other proteins contribute to the neuronal damage (Cookson, 2006).

Alpha-synuclein is hypothesized to affect the mitochondria, leading to cell death; it is also hypothesized to affect net sensitivity to cell death, and to include toxins. A mitochondrial enzyme was reported as similar to the alpha-synuclein binding cytochrome c oxidase; however no evidence was found on how the predominantly cytoplasmic alpha-synuclein gains access to the inner mitochondrial membrane (IMM) (Cookson, 2006; Elkon et al., 2002). Alpha-synuclein has an important role in synaptic plasticity, regulation of dopaminergic neurotransmission, and synaptic vesicle turnover. Alpha-synuclein is a natively unfolded protein that, binding to lipids, can form oligomeric or amyloidogenic filaments. In its fibrillar form it is the main component of LBs. Alpha-synuclein-mediated toxicity in neurodegenerative diseases is due more to soluble intermediate oligomer fractions than to fibrillar deposits. A toxic gain of function of mutant alpha-synuclein and its overexpression are related to the pathology. Researchers have shown that missense mutations, multiplications and inducible expression (p.Ala30Pro SNCA) decreased proteasome activity and increased both the sensitivity to mitochondria-dependent apoptosis and the overexpression of mutant forms of alpha-synuclein (p.Ala53Thr SNCA), leading to mtDNA damage and degeneration. The pathogenic sequences (Glu46Lys, p.Ala53Thr SNCA and p.Ala30Pro SNCA) are toxic for the autophagy-lysosome systems because they block the degradation of other chaperone-mediated autophagy substrates (Bogaerts et al., 2008). As a result, alpha-synuclein has a key role in dopaminergic neuronal cell death since it is the major structural component of LBs (Branco et al., 2010).

The protective role of *parkin*, *PINK1*, *DJ-1*, and *LRRK2* in mitochondrial function is important in DLB. *Parkin* has a cytoplasmic localization on the outer mitochondrial membrane (OMM) and it works as an E3 ubiquitin ligase. Its mutations (missense, nonsense and frameshift, intraexonic deletions, insertions, promoter and exon deletions and multiplications) support the hypothesized role of parkin in mitochondrial functions. In fact, parkin mutations have been found to lead to loss of the protective role of parkin against apoptosis and to decreased levels of cellular reactive oxygen species (ROS) in mitochondria. Mitochondrial dysfunction and oxidative stress, on the contrary, affect parkin function, as shown in the presence of nitrosative stress combined with a single parkin mutation. This emerges clearly in the heterozygous associated with sporadic form (Bogaerts et al., 2008). Pink1 is a mitochondrial kinase mainly localized in the IMM and it has an N-terminal mitochondrial-targeting motif that exerts its neuroprotective effect by phosphorylating specific mitochondrial proteins and, in turn, modulating their functions. In short, its inactivation can induce neuronal death via an oxidative stress pathway (Wang and Youle, 2009). Its overexpression protects cells against apoptosis occurring via the mitochondrial pathway, whereas pathogenic mutations of PINK1 in the kinase domain (E240K, L489P, K219M) disrupt this protective function (Petit-Paitel, 2010). However, its physiological substrates remain unknown.

DJ-1 is expressed in a variety of tissues and is partially localized in the mitochondrial matrix and intermembrane space. Protecting against oxidative injury (it is putatively able to sense oxidative stress), it acts as a detector of ROS. At transcriptional level (DJ-1 binds to PIAS proteins, a family of SUMO-1 ligases that modulates the activity of various transcription factors), there are other protective and transcriptional co-activator factors that interact with the nuclear proteins against apoptosis. DJ-1 also stabilizes the anti-oxidant transcriptional master regulator Nrf2 (located in the nucleus of SN neurons) by preventing association with its inhibitor protein KEap1. In the same pathway, modification of cysteine sulfinic acid might enhance its association with mitochondria, while oxidative stress promotes the interaction of mutated cysteine residues with parkin, linking DJ-1 and parkin (Ahlskog, 2009; Taira et al., 2004).

LRRK2 resides throughout the cytosol but also associates with the OMM; its domains include a leucine-rich repeat domain and a GTPase domain. Mutations in *LRRK2* cause autosomal dominant late-onset PD and missense mutations have been reported along with proteins that increased apoptosis (MacLeod et al., 2006).

In this review, we identified other genes related to mitochondrial function and oxidative stress that are implicated in DLB: the genes encoding the main dopamine metabolism enzymes (MAO-A and MAO-B) and HtrA2. DA metabolism plays a role both in alpha-

synuclein aggregation and in the stabilization of alpha-synuclein protofibrils.
Higher proportions of mtDNA molecules carrying deletions are found in homogenates of the SN and dorsal striatum than in other brain regions (Soong et al., 1992) and high levels of mtDNA deletions can cause degeneration of dopaminergic neurons (Sterky, 2012) and may result in their loss. Dopaminergic neurons show a specific sensitivity to mitochondrial stress because DA is very unstable. Indeed, DA is synthesized in the cytosol and rapidly pumped into synaptic spaces. It is easy to understand how defects of the secretory pathway or OXPHOS increase cytosolic DA levels and consequently ROS production.
HtrA2 is a serine protease with a pro-apoptotic function. It is important for mitochondrial homeostasis, and its cellular localization is in the intermembrane space. It can be released from the mitochondria during apoptosis and it tries to mimic caspases so that it may be recruited by IAP-caspase inhibitors (such as XIAP and CIAP1/2). XIAP is an x-linked inhibitor of apoptosis (IAP) and a member of the IAP family of proteins. HtrA2 cleaves the IAP, reducing the cell's inhibition to caspase activation. Researchers have identified the p.Gly399Ser mutation in HtrA2 in patients with sporadic PD. This pro-apoptotic function is important at this cellular level because the mutations caused by the mitochondrial swelling impair the regulation of proteolytic activity and decrease mitochondrial membrane potential (Mandemakers et al., 2007).

Dysfunction of mitochondrial energy metabolism in neurons

Neurons have high energy demands and mitochondria are concentrated in specific cell regions: axon, dendritic spines, and pre- and postsynaptic sites. Mitochondrial dynamics (fusion and fission) determine the localization of mitochondria to axon terminals and their distribution in dendrites. Inhibition of fission causes dendritic elongation and decreases the density of dendritic spines and the numbers of mitochondria in these sites. On the other hand, increased fission facilitates the mobilization of dendritic mitochondria and leads to an increase in the number of dendritic spines. Dysfunction of mitochondrial energy metabolism (Fig. 1) leads to reduced adenosine triphosphate (ATP) production, impaired calcium buffering, and increased generation of ROS; oxidative damage to mitochondria has been shown to impair mitochondrial function and lead to cell death via apoptosis and necrosis (Perry et al., 2002; Beal, 2005; Youle and Karbowski, 2005; Detmer and Chan, 2007).
The brain is vulnerable to oxidative damage and ROS. A vicious cycle characterizes the production of ROS: dysfunctional mitochondria will produce more ROS, and this leads to the establishment of a feed-forward loop, because ROS mediate mitochondrial oxidative damage, which leads to generation of more ROS.
Alpha-synuclein may accumulate as a result of either rare genetic mutations or post-translational changes,

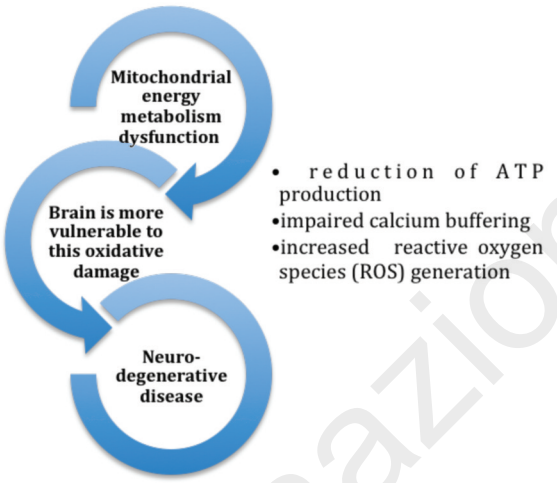

Figure 1 - Mitochondria and neurodegeneration.
Mitochondria are crucial checkpoints of tissue homeostasis and their alteration leads to both cell damage and impaired metabolism. A mitochondrial energy metabolism dysfunction causes reduction of ATP production, impaired calcium buffering and increased generation of reactive oxygen species (ROS). The brain is particularly vulnerable to this oxidative damage and ROS is a cause of neurodegenerative diseases.

mainly due to oxidative/nitrosative stress, probably related to sporadic neurodegenerative disease forms. Mutations of alpha-synuclein can, through different mechanisms, lead to alteration of mitochondrial functions but, alternatively, mitochondria can be damaged by environmental toxins, such as rotenone or MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a synthetic by-product of heroin) (Perry et al., 2002; DiMauro, 2007; Hölinger et al., 2006).

Discussion and concluding remarks

Mitochondrial mechanisms in DLB

The aim of this study was to identify, through a systematic review of the scientific literature, mitochondrial mechanisms potentially involved in DLB pathogenesis. It emerged that the main mitochondrial mechanism involved in DLB pathogenesis is related to the relationship that exists between mitochondria and alpha-synuclein: mitochondrial malfunction due to oxidative stress may lead to DLB, and mitochondrial damage is due to alpha-synuclein. There is also another neurotoxic mechanism involved in the possible genesis of LBs: that of toxic DA metabolites. This mechanism plays a role both in alpha-synuclein aggregation and in the stabilization of alpha-synuclein protofibrils.
As already indicated, dopaminergic neurons show a specific sensitivity to mitochondrial stress because DA is very unstable and generates ROS and, via monoaminoxidase, produces H_2O_2 through the SLC18A2 system (vesicular monoamine transporter 2). DA is synthesized in the cytosol and rapidly pumped into synaptic spaces. It is easy to understand how defects

of the secretory pathway or OXPHOS increase cytosolic dopamine levels and consequently ROS production. Different levels of alpha-synuclein oligomerization have been linked to cell death; in fact, a mixture of oligomers of alpha-synuclein can lead to calcium dysregulation (Surmeier et al., 2011), probably via a pore-forming mechanism. Both calcium dysregulation and fibril deposition are characterized by a vicious cycle that eventually leads to severe calcium overload. This has two consequences: the reaching of the point of mitochondrial permeability transition and the commitment to neuronal cell death (Lashuel et al., 2002). It is necessary to consider the important role played by calpain (calcium-activated protease) in cleaving alpha-synuclein and in protofibril formation. The UPS is the primary mechanism in alpha-synuclein degradation and it could be inhibited by alpha-synuclein protofibrils. The excessive ROS/RNS formation associated with these processes may induce UPS impairment and/or misfolding of molecular chaperones, resulting in protein aggregation and neuronal damage. Damage to the respiratory chain complex I and excessive calcium influx due to activation of NMDA-type glutamate receptors in the nervous system (with activation of neuronal NO synthase) are the main sources of ROS in cells. The second neurotoxic mechanism could take place at a GSK-3 beta level. Activation of GSK-3 beta determines the phosphorylation and aggregation of alpha-synuclein in LBs and the low activity of the mitochondria involved. Different environmental toxins can activate this kinase, such as: MPTP, pesticides, neurotoxins, 6-hydroxydopamine. Activation of this kinase by neurotoxins may occur by two different reactions: i) the mitochondrial membrane potential becomes lower and consequently the membrane pores open, causing the cytochrome c to enter the cytosol. This determines the activation of a caspase cascade, with DNA fragmentation and cell death by apoptosis, followed by neurodegeneration; ii) facilitation of alpha-synuclein and synphilin-1 aggregation in the LBs.

Finally, another important neurotoxic mechanism is the specific sensitivity of dopaminergic neurons to mitochondrial stress. DA is an important neurotransmitter involved in many aspects of neural function, including motor activity, emotion, reward, sleep and learning (Jackson and Westlind-Danielsson, 1994). Although it has been suggested that the effects of DA in disorders such as DLB, PD and schizophrenia are linked to impaired mitochondrial function (Thomas and Beal, 2007), an influence of DA on mitochondrial movement has not been clearly reported (Chen et al., 2008). In view of these considerations, we decided to investigate the effect of DA on mitochondrial trafficking. It has been noted in earlier studies that a homeostatic distribution of mitochondria in peripheral regions of neurons (in particular axons and dendrites) is critical for maintaining proper neuronal function (Soong et al., 1992). Striking a balance between motile (that is, both directionally moving and oscillatory) and stationary populations of mitochondria may therefore be important for sustaining neuronal activity. Indeed, in the axons of hippocampal neurons, large shifts in motile and non-motile mitochondrial populations have been shown to cause dramatic changes in levels of synaptic activity (Sterky, 2012). The results of the present study seem to show a close involvement of mitochondrial dysfunctions and suggest that DA is implicated in the pathogenesis of DLB: DA may serve to limit the redistribution of potential energy sources in neurons and it plays a role both in alpha-synuclein aggregation and stabilization of alpha-synuclein protofibrils.

The above literature evidence links mitochondrial malfunction with neurodegenerative diseases and, as seen in this review, with DLB. In DLB, A-beta-42 (an amyloid precursor) may promote alpha-synuclein accumulation and neurodegeneration. The mechanism by which this occurs is not completely clear but recent advances suggest that nerve damage might result from the conversion of non-toxic monomers to toxic oligomers and protofibrils. This mechanism is currently under investigation, but several lines of evidence support the possibility that A-beta peptide and alpha-synuclein might interact to cause mitochondrial and plasma membrane damage upon translocation of protofibrils to the membranes (Hashimoto et al., 2003). Accumulation of beta- and alpha-synuclein oligomers in the mitochondrial membrane might result in the release of cytochrome c with the subsequent activation of the apoptotic cascade. LBs are found in a number of neurodegenerative disorders (Hashimoto et al., 1999; Hsu et al., 2000; Gardner et al., 2007) that occur increasingly with aging, namely PD, AD, LBD, and in a number of hereditary disorders. LBs have been considered to be toxic, protective, or innocuous. If they are protective, an increasing number of LB-laden neurons is not seen in the nervous system. Mitochondria produce ATP for the cell and are central to apoptosis. The mitochondrion is composed of: the outer membrane, the intermembrane space, the inner membrane and the matrix. On account of its role in the production of bio-energy for cells, the mitochondrion has evolved to play a central role in apoptosis through the release of proapototic molecules from the intermembrane space (Wang and Youle, 2009; Youle and Karbowski, 2005).

Further studies are required for a better understanding of the mechanisms favoring alpha-synuclein aggregation and the specific mechanism of aggregate toxicity.

Future investigations could focus on genes involved in a common mitochondrial pathway. It would be interesting to discover a protein map and to establish gene-protein functional interactions between mitochondria and LBs. Such a map might provide the key that would make it possible to examine dynamic mitochondrial deregulation. This may, in turn, contribute to current knowledge of mitochondrial function in the field of neuropsychiatry, and help to address the open issue of whether the mitochondria have tissue-specific features.

Finally, the authors wish to draw attention to the fact that new therapy targets might be developed from animal models of mitochondrial neurodegeneration.

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