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Review

Neurochemistry and the non-motor aspects of PD

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ABSTRACT

Parkinson disease (PD) is a systemic disease with variegated non-motor deficits and neurological symptoms, including impaired olfaction, autonomic failure, cognitive impairment and psychiatric symptoms, in addition to the classical motor symptoms. Many non-motor symptoms appear before or in parallel with motor deficits and then worsen with disease progression. Although there is a relationship, albeit not causal, between motor symptoms and the presence of Lewy bodies (LBs) and neurites filled with abnormal α-synuclein, other neurological alterations are independent of the amount of α-synuclein inclusions in neurons and neurites, thereby indicating that different mechanisms probably converge in the degenerative process. This may apply to complex alterations interfering with olfactory and autonomic nervous system functions, emotions, sleep regulation, and behavioral, cognitive and mental performance. Involvement of the cerebral cortex leading to impaired behavior and cognition is related to several convergent altered factors including: a. dopaminergic, noradrenergic, serotoninergic and cholinergic cortical innervation; b. synapses; c. cortical metabolism; d. mitochondrial function and energy production; e. oxidative damage; f. transcription; g. protein expression; h. lipid composition; and i. ubiquitin–proteasome system and autophagy, among others. This complex situation indicates that multiple subcellular failure in selected cell populations is difficult to reconcile with a reductionistic scenario of a single causative cascade of events leading to non-motor symptoms in PD. Furthermore, these alterations may appear at early stages of the disease and may precede the appearance of substantial irreversible cell loss by years. These observations have important implications in the design of therapeutic approaches geared to prevention and treatment of PD.

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Introduction

Parkinson disease (PD) is characterized clinically as a complex motor disorder manifested by resting tremor, slowness of initial movement, rigidity and general postural instability, and pathologically by loss of dopaminergic neurons in the substantia nigra pars compacta, leading to reduced dopaminergic input to the striatum, and accompanied by adaptative responses in the internal and external globus pallidus, subthalamus, thalamus and substantia nigra pars reticularis. Round, hyaline neuronal cytoplasmic inclusions called Lewy bodies (LBs) and enlarged aberrant neurites (LNs) and threads are found in the substantia nigra and other nuclei such as the locus ceruleus, reticular nuclei of the brain stem, and dorsal motor nucleus of the vagus, as well as the basal nucleus of Meynert, the amygdala and the CA2 area of the hippocampus (Braak and del Tredici, 2008; Braak et al., 1999; Dickson, 2001; Dickson et al., 2009a,b; Forno, 1996; Goedert 2001; Jellinger and Mizuno, 2003).

Dementia with Lewy bodies (DLB) is clinically manifested as dementia with parkinsonism or as parkinsonism followed by dementia. Pathologically, DLB is characterized by lesions typical of PD together with widespread distribution of LBs and LNs in the cerebral cortex and diencephalic nuclei (Galvin et al., 2001; Ince and McKeith, 2003; Irizarry et al., 1998; McKeith et al., 2004; Spillantini et al., 1998). Because of the presence of LBs, PD and DLB are considered *Lewy body diseases* (LBDs).

DLB may occur with no or with scarce amyloid plaques, and then it is considered DLB pure form, whereas DLB with accompanying neurofibrillary tangles and senile plaques is called DLB common form (Kosaka, 1990, 1993). Among DLB cases, brains of the subtype showing severe AD pathology correspond to brains with advanced Lewy pathology, suggesting that AD pathology exacerbates Lewy pathology (Marui et al., 2002).

LBs and LNs are composed of aggregates of normal, misfolded and truncated proteins, p62 and ubiquitin, all of which are stored in the cytoplasm as non-degraded by-products of the degenerative process (Leverenz et al., 2007; Schults, 2006; Wakabayashi et al., 2007; Xia et al., 2008). The main component of LBs and aberrant neurites is α-synuclein which is abnormally phosphorylated, nitrated and oxidized, has an abnormal crystallographic structure and abnormal solubility, and is prone to the formation of aggregates and insoluble fibrils (Anderson et al., 2006; Baba et al., 1998; Duda et al., 2000; Fujiwara et al., 2002; Giasson et al., 2002; Hashimoto and Masliah, 1999; Iwatsubo, 2003; Spillantini et al., 1997; Wakabayashi et al., 1998). Based on these molecular characteristics LBDs are categorized as α-synucleinopathies.

Genetics of PD and DLB

Mutations (A53T, A30P, E46K) in the α-synuclein gene or *SNCA* are causative of autosomal dominant PD (Krüger et al., 1998; Polymeropoulos et al., 1997; Zarranz et al., 2004). In addition, duplication or triplication of the α-synuclein locus is associated with PD (Chartier-Harlin et al., 2004; Ibanez et al., 2004; Nishioka et al., 2006; Singleton et al., 2003). Yet studies in vitro have shown that E46K, A30P, A53T and A30P/A53T mutations of α-synuclein have different, opposing effects regarding oligomerization and fibrillation of α-synuclein at early stages of α-synuclein assembly (Ono et al., 2011). Therefore, the mechanism of mutant synucleins in the pathogenesis of LBs is not fully understood.

Methylation of the human *SNCA* intron 1, which decreases *SNCA* gene expression, is reduced in substantia nigra, putamen and cerebral cortex in PD, suggesting activation of *SNCA* in PD (Jowaed et al., 2010). α-synuclein also appears to be regulated post-transcriptionally by microRNAs mir-7 and mir-153, which bind specifically to the 3′-untranslated region of α-synuclein and down-regulate its mRNA and protein levels, thus decreasing endogenous expression of α-synuclein (Doxakis, 2010; Junn et al., 2009). The miRNA-433 binding site of fibroblast growth factor 20 may confer risk for PD by overexpressing α-synuclein (Wang et al., 2008).

Mutations in *parkin* (*PARK2*) (Kitada et al., 1998), *DJ1* (*PARK7*) coding for Parkinson disease protein 7 (Bonifati et al. (2003), *PINK1* (*PARK6*) coding for PTEN-induced putative kinase 1 (Valente et al., 2004), *LRRK2* (*PARK8*) coding for leucine-rich repeat kinase 2 (Paisanz-Ruiz et al., 2004; Zimprich et al., 2004), and *HTRA2* (*PARK13*) coding for HtrA serine peptidase 2: HtrA2 (Strauss et al., 2005) may be causative of PD. Another gene involved in familial PD is *UCHL1* (*PARK5*) coding for ubiquitin carboxyl-terminal hydrolase L1 (Leroy et al., 1998). A strong association between galactocerebrosidase mutations and PD has also been reported (Sidransky et al., 2009). Additonal loci associated with autosomal and recessive PD have been described (Gasser, 2009; Hardy et al., 2009; Thomas and Beal, 2007).

Mutations in *SNCA* result in LB formation. Mutation in *PINK1* is also associated with LB pathology similar to that seen in sporadic PD (Samaranch et al., 2010). Yet not all familial cases with PD due to *parkin* and *LRRK2* mutations have LBs, although all of them have predominant degeneration of the substantia nigra pars compacta (Santpere and Ferrer, 2009). Therefore, PD cases due to *parkin* and *LRRK2* mutations without LBs cannot be considered as instances of LBD. Whether α-synuclein is altered in these conditions will be discussed below.

Genetic studies have shown that DLB may be due to mutations in α-synuclein and LRRK2. PD and DLB occured in a family with the E46K mutation in *SNCA* (Zarranz et al., 2004), and mutations in *LRRK2* have been associated with a range of clinical phenotypes including PD and DLB (Zimprich et al., 2004). Other genes involved in DLB are *GBA* (gene encoding glucocerebrosidase) (Goker-Alpan et al., 2006; Mata et al., 2008) and *PSN1* encoding presenilin 1 (Ishikawa et al., 2005). Genetic studies in some families with DLB have failed to uncover the cause of the disease (Clarimón et al., 2009).

Proteins encoded by genes causing genetic PD or DLB have different and variegated functions. Some of them are related with mitochondria

and energy metabolism, whereas others are linked to the ubiquitin–proteasome system (UPS). Others are not known to have relations with synuclein and related molecules. These facts point to the likelihood that PD and DLB are biological processes triggered by multiple and diversified pathways.

Finally, but not less important, effects of gender in differential gene expression have been found in the normal and PD substantia nigra, and in animal models (Cantuti-Castelvetri et al., 2007; Yacoubian et al., 2008). Other reports have not encountered gender differences, probably because of the unbalanced proportion of males in these studies (Simunovic et al., 2009). Functional studies have also shown estradiol modulation of 5-hydroxytryptamine receptors in several brain regions of female hemiparkinsonian monkeys after long-term ovariectomy (Sánchez et al., 2011). Together, these observations point to the likelihood that the pathogenesis of sporadic PD is subjected to genetic factors linked to gender differences.

Stages of PD-related pathology

Systematic study of cases with LB pathology has prompted a staging classification of PD based on the putative progression of LB pathology from the medulla oblongata (and olfactory bulb) to the midbrain, diencephalic nuclei, and neocortex (Braak et al., 2002; Braak et al., 2003; Braak et al., 2004). Stage 1 is characterized by LBs and neurites in the dorsal IX/X motor nuclei and/or intermediate reticular zone; there is also myentheric plexus involvement. Stage 2 affects the medulla oblongata and pontine tegmentum and covers pathology of stage 1 plus lesions in the caudal raphe nuclei, gigantocellular reticular nucleus, and ceruleus–subceruleus complex; the olfactory bulb is also involved. Stage 3 refers to pathology of stage 2 plus midbrain lesions, particularly in the pars compacta of the substantia nigra. Stage 4 includes basal prosencephalon and mesocortex pathology (cortical involvement confined to the transentorhinal region and allocortex, and CA2 plexus) in addition to lesions in the midbrain, pons and medulla oblongata. Stage 5 extends to sensory association areas of the neocortex and prefrontal neocortex. Stage 6 includes, in addition, lesions in first order sensory association areas of the neocortex and pre-motor areas; occasionally there are also mild changes in primary sensory areas and the primary motor field.

Several atypical cases not following a clear gradient of LB pathology from the medulla oblongata to the neocortex constitute from 5 to 10% of total LBDs (Braak et al., 2006a,b; Jellinger, 2004, 2008, 2009).

Incidental PD, pre-motor PD (pre-motor LBD)

Cases with LB pathology in the brain stem without parkinsonism are considered incidental PD (iPD) (Ferrer et al., 2011b; Jellinger, 2004; Saito et al., 2004). Whether these cases constitute presymptomatic PD has been a matter of controversy for years. However, clinical and neuropathological studies have yielded a solid basis of learning indicating that PD should no longer be considered as a disorder characterized solely by parkinsonism. Rather, thinking about PD has evolved, and it is now seen as a brain disease with disparate manifestations such as olfactory dysfunction, dysautonomia, sleep fragmentation, rapid eye movement behavior disorder, mood and anxiety disorders, and depression, with most of these appearing before parkinsonian symptoms and signs (Ziemssen and Reichmann, 2007). For these reasons, iPD with clinical symptoms without parkinsonism is now considered as pre-motor PD (Dickson et al., 2008; Ferrer et al., 2011b). This is further reinforced by the observation of striatal dopaminergic deficits in the striatum in iPD (DelleDonne et al., 2008; Ferrer et al., 2011b). Yet some incidental LBD cases have LBs in the cerebral cortex and these cases have been categorized as putative preclinical stages of DLB (Frigerio et al., 2011).

Amygdala-predominant LBD

LBs and LNs are commonly found in the amygdala but are usually absent in the brainstem in sporadic and familial AD, Down syndrome and other tauopathies (Hamilton, 2000; Lippa et al., 1999; O'Connell et al., 1998; Popescu et al., 2004; Yamazaki et al., 2000; Yokota et al., 2007). For this reason, LB pathology almost restricted to the amygdala in AD (and Down syndrome and other tauopathies) has been categorized as a distinct α-synucleinopathy (Uchikado et al., 2006), probably related to factors inherent to AD and to the selective vulnerability of the amygdala in AD and LBDs (Dickson et al., 2010). Intriguingly, α-synuclein inclusions also occur in the olfactory bulb and tract in cases of AD with amygdala-predominant LB pathology (Fujishiro et al., 2008a,b).

LBs and LNs are associated with α-synuclein-immunoreactive pleomorphic neuronal inclusions and dystrophic neurites around β-amyloid plaques in these cases (Parkkinen et al., 2003; Uchikado et al., 2006; Wirths et al., 2000). Double-labeling immunofluorescence and confocal microscopy disclose partial co-localization of hyper-phosphorylated tau and α-synuclein in dystrophic neurites of senile plaques in these cases (Fig. 1), thus indicating overlap of hyper-phosphorylated tau and α-synuclein pathology in amygdala-predominant α-synucleinopathy associated with AD, as already described in certain α-synucleinopathies (Arima et al., 1999; Duda et al., 2002; Ishizawa et al., 2003; Kotzbauer et al., 2004; Terni et al., 2007). Yet pathological modifications of α-synuclein in these cases are similar to those seen in common PD and other LBDs. α-synuclein is abnormally hyper-phosphorylated at Ser129, and nitrated (Fig. 2) Together, these observations show that the characteristics of α-synuclein, including abnormal solubility and aggregation, and phosphorylation, lipoxidation and nitration, are similar in amygdala-predominant α-synucleinopathy and in other LBDs.

Non-motor symptoms in PD

Dysautonomia (including altered vascular/circulatory, digestive and urinary performances), olfactory dysfunction, sleep disorders (sleep fragmentation, rapid eye movement behavior disorder and complex paroxysmal nocturnal motor behavioral) and mild to severe psychiatric disorders are common in PD; moderate or mild cognitive debilitation are found in PD (Boeve, 2010; Chaudhuri et al., 2005; Goetz et al., 2010; Goldstein et al., 2010; Goldstein et al., 2011; Herting et al., 2008; Iranzo et al., 2006; Lang, 2011; Lim et al., 2009; Manni et al., 2010; Morley and Duda, 2010; Müller et al., 2011; Natale et al., 2008; Oh et al., 2011; Poewe, 2007; Poewe, 2008; Postuma et al., 2006; Ross et al., 2008; Sharabi and Goldstein, 2011; Siderowf and Stern, 2006; Tolosa et al., 2007; Videnovic and Comella, 2011; Wolters and Braak, 2006; Ziemssen and Reichmann, 2007).

Anhedonia, apathy, anxiety, panic attacks, social phobias and depression occur in patients with PD even at early pre-motor stages and unrelated to medication (McKinlay et al., 2009; Pedersen et al., 2009; Poewe, 2008). Visual and auditory hallucinations, agitated confusion, vivid dreaming, delirium and delusions are common in PD (Doe De Maindreville et al., 2005; Inzelberg et al., 1998; Papapetropoulos and Mash, 2005; Sanchez-Ramos et al., 1966; Wolters, 2001).

All these alterations may precede parkinsonian symptoms by decades (Claassen et al., 2010), and they usually increase in intensity with disease progression. Even neuropsychiatric alterations and cognitive decline may occur at early stages of parkinsonism, suggesting that they are an integral part of PD from the beginning of the disease in some patients. Characteristically, symptoms are often subtle at the beginning and difficult to detect without neuropsychological tests, although they become aggravated with progression of the disease. Deficits mainly affect executive function including working memory and visuospatial capacity. These are often accompanied by anxiety and depression, and excessive daytime sleepiness (Kulisevsky et al., 2008).

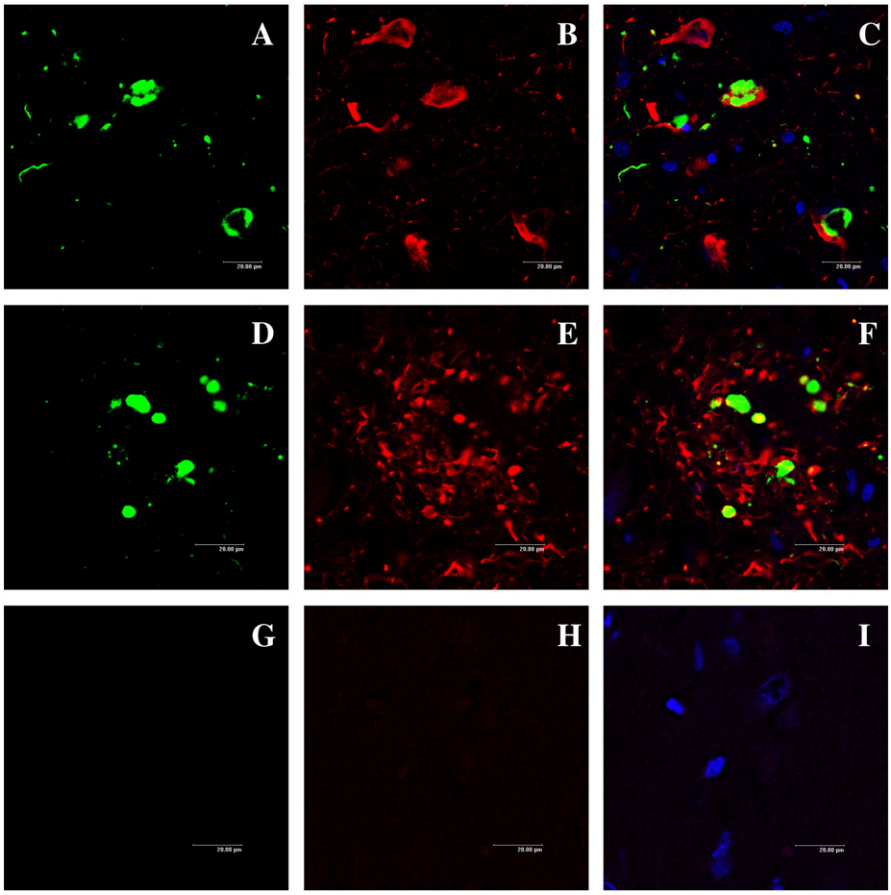

Fig. 1. Double-labeling immunofluorescence and confocal microscopy. A–C: Anti-α-synuclein (green) and phospho-tau (AT8: red) co-localize (merge: yellow) in a subset of neurons and neurites in the amygdala of AD cases with amygdala-predominant Lewy pathology. D–F: βA-immunoreactive plaques (green) are surrounded by α-synuclein-immunoreactive aberrant neurites (red). C–F: Merge. G–I: Negative control following incubation without the primary antibodies. Nuclei are stained with DRAQ5 (blue).

Non-motor symptoms also occur in familial PD but they appear to be more benign in certain familial cases linked with LRRK2 or parkin mutations than in sporadic PD (Alcalay et al., 2011; Healy et al., 2008; Kägi et al., 2010; Somme et al., 2011; Yoritaka et al., 2011).

Finally, the peripheral nervous system is also affected in PD even at early stages of the disease and without any relation to peripheral nerve complications associated with the treatment of PD (Ikemura et al., 2008; Nolano et al., 2008). This is further sustained by the observation of mixed peripheral neuropathy in familial cases bearing LRRK2 mutations preceeding motor symptoms (unpublished observations).

The main pathological findings of non-motor symptoms are related to α-synuclein deposition (Dickson et al., 2009a,b) which is abnormally hyper-phosphorylated (Beach et al., 2010). Yet several aspects are still elusive and need further study: i. Autonomic symptoms are not always present in PD; ii. LB pathology in autonomic peripheral ganglia and plexus is not always associated with clinical symptoms; iii. Little is known about the nature and composition of LBs in peripheral autonomic nervous system; iv. No data are available about molecular changes preceding, or associated with, early and late stages of LB pathology in the autonomic peripheral nervous system; and, v. Little is known about alterations other than the accumulation of abnormal α-synuclein that may be causative of altered function related to olfaction, impaired autonomic function, sleep disorders, and altered behavior in PD (Ferrer et al., 2011b).

Lack of correlation between α-synuclein aggregates in the form of LBs and impaired function is dramatically exemplified in relation with cognitive and mental functions. Retrospective clinical and pathologic studies have shown that there is no relationship between LB stage and severity of cognitive impairment in advanced stages of PD (Jellinger, 2008, 2009; Parkkinen et al., 2008; Parkkinen et al., 2005a,b; Weisman et al., 2007). These and other studies have led to the visualization of PD as a systemic disease in which functional deficits are not exclusively related with LB pathology in neurons and neurites (Ferrer, 2009a,b, 2011).

It is worth stressing that the occurrence of non-motor symptoms at pre-motor stages of PD has direct implications in the early diagnosis of the disease. Impaired olfaction, autonomic nervous system dysfunction, and sleep disorders can be monitored and may serve as putative markers of the disease considering that causes of olfactory deficience are not rare with age and they often related to variegated local and neurological disorders; similar considerations can be made for the other symptoms. Yet combined olfaction tests, polysomnographic studies, ECG registers and other sophisticated methods can be used to identify possible affected individuals (Iranzo, 2011; Lang, 2011; Marek and Jennings, 2009; Valappil et al., 2010). Whether and when individuals suffering from one of these symptoms should be subjected to neuroimaging functional studies of the nigrostriatal system is a matter of clinical controversy. Nevertheless, it is reasonable that symptoms, pathology and physiology of the cardiovascular, skin/sweat gland, urinary, gastrointestinal, pupillary and neuroendocrine systems can be examined by biopsy and non-invasive electrophysiological techniques to assess autonomic anatomy and function in PD (Jain, 2011). On the other hand, total α-synuclein levels are not modified in peripheral blood cells when compared with controls, nitrated α-synuclein expression levels are increased in PD (Prigione et al., 2010). However, it is not known whether this alteration is detectable at pre-motor stages of PD.

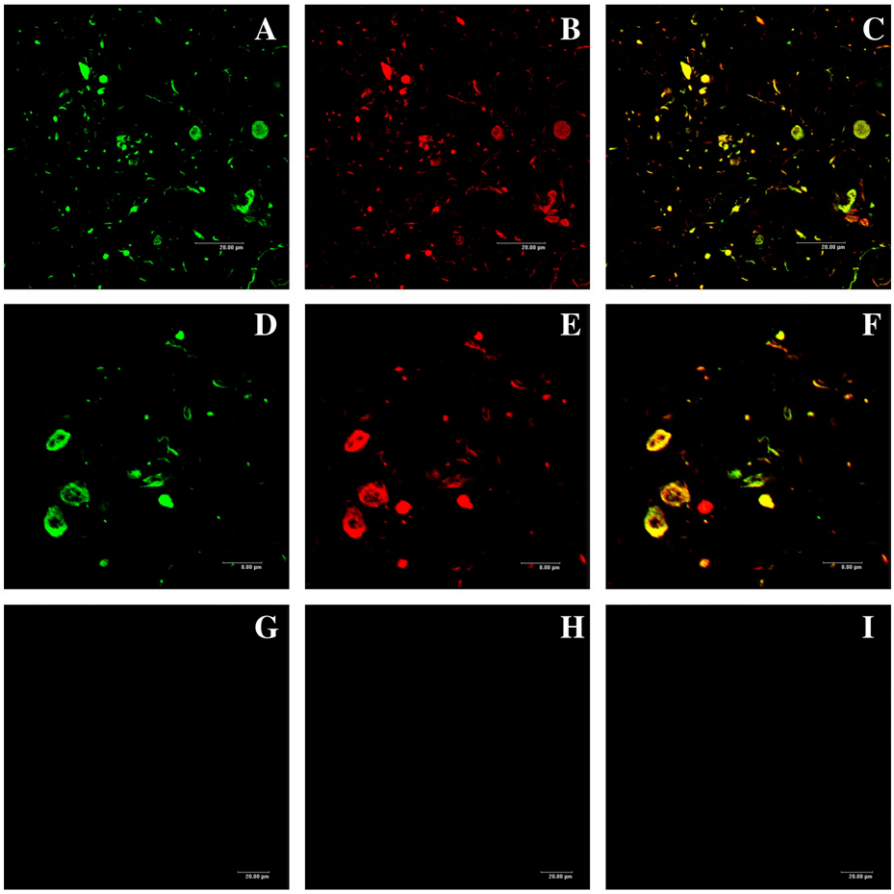

Fig. 2. A–C: Double-labeling immunofluorescence and confocal microscopy showing anti-α-synuclein (green) and anti-phosphorylated-α-synucleinSer129 (red) co-localization (merge: yellow) in a subset of aberrant neurites in the amygdala of AD cases with amygdala-predominant Lewy pathology. D–F: α-synuclein (green) and nitrated α-synucleinSer129 (red) co-localization (merge: yellow). G–I: Negative control following incubation without the primary antibodies.

The sequence and time-scales of the different non-motor symptoms in PD is variable from one patient to another. However, olfactory disturbances and autonomic failure may precede for decades the appararance of motor symptoms. Patients with the idiopathic form of REM sleep behavior disorder with decreased striatal dopamine transporters imaging, substantia nigra hyperechogenicity and hyposmia have an increased short-term risk for developing the classical motor symptoms of PD (Iranzo, 2011).

Dysautonomia

Functional studies using 123I meta-iodobenzylguanidine (MIBG) myocardial scintigraphy have shown reduced MIBG uptake in PD (Kashihara et al., 2006; Mitsui et al., 2006; Oka et al., 2007; Sawada et al., 2009; Stiasny-Kolster et al., 2005; Takatsu et al., 2000). Decreased MIBG uptake may precede neuronal loss in the sympathetic ganglia (Orimo et al., 2005; Orimo et al., 2007; Orimo et al., 2008). Cardiac sympathetic denervation precedes nigrostriatal loss in individuals bearing the E46K mutation in *SNCA* (Tijero et al., 2010). However, loss of cardiac innervation may also present in parallel with dopaminergic deficits in the putamen, as revealed with PET, or may even occur at advanced stages of the disease (Goldstein et al., 2011).

Alterations implicate both tyrosine hydroxylase-positive (extrinsic) and negative (intrinsic) nerves of the cardiac plexus (Fujishiro et al., 2008a,b; Iwanaga et al., 1999). Decreased tyrosine hydroxilase immunoreactivity in nerve fibers was already observed in the two individuals examined with iPD (Ghebremedhin et al., 2009). Accumulation of α-synuclein aggregates occurs in the distal axons of the cardiac sympathetic nervous system preceding that of neuronal somata or neurites in the paravertebral sympathetic ganglia, thereby suggesting a centripetal degeneration of the cardiac sympathetic nerve in PD (Orimo et al., 2008).

LBs, and more often small α-synuclein cytoplasmic and neuritic inclusions, are present in the parasympathetic ganglia, sympathetic ganglia, and enteric nervous system in PD (Takeda et al., 1993; Wakabayashi et al., 1990). These are consistently found in the hypothalamus, sympathetic (intermediodorsal nucleus of the thoracic cord and sympathetic ganglia) and parasympathetic system (dorsal vagal and sacral parasympathetic nuclei, and peripheral parasympathetic ganglia), as well as the enteric plexus (Hague et al., 1997; Micieli et al., 2003; Wakabayashi and Takahashi, 1997). Regarding central medullary autonomic areas, raphe neurons are reduced in number with disease progression (Benarroch et al., 2005). Neuropathological studies in large cohorts of neurologically unimpaired aged individuals have shown that the autonomic nuclei of the spinal cord and the peripheral autonomic nervous system are affected early on by LB pathology (Bloch et al., 2006; Mínguez-Castellanos et al., 2007; Oinas et al., 2010; Probst et al., 2008). α-synuclein-immunoreactive inclusions are seen in neurons of the Meissner's and Auerbach's plexuses and in the corresponding axons projecting into the mucosa (Braak et al., 2006a,b; Wakabayashi et al., 1988).

Immunohistochemical methods to detect phosphorylated α-synuclein have revealed multi-organ localization and gradient distribution of aberrant α-synuclein deposits. The highest densities occur in the spinal cord, paraspinal sympathetic ganglia, vagus nerve, gastrointestinal tract, and endocrine organs. Within the gastrointestinal tract, the lower esophagus and the submandibular gland show higher numbers of inclusions than the colon and rectum (Beach et al., 2010).

Olfactory dysfunction

α-synuclein pathology affecting neurons and neurites occurs in the olfactory bulb and related olfactory nuclei at very early stages of PD-related pathology (Bloch et al., 2006; Braak et al., 2003, 2004; Daniel and Hawkes, 1992; Del Tredici et al., 2002; Hubbard et al., 2007; Pearce et al., 1995). Curiously, double-labeling immunohistochemical studies have shown that mitral cells, calcium-binding protein- and substance-P-positive cells are vulnerable, whereas dopamine- and somatostin-positive cells are rarely affected (Ubeda-Bañon et al., 2010). Moreover, dopaminergic periglomerular neurons in olfactory bulb in PD are more readily preserved (Mundiaño et al., 2011). Whether modifications in the number of neurons in the PD olfactory bulb is partly due to altered neurogenesis, as observed in animal models (Lelan et al., 2011; O'Keeffe et al., 2009) deserves further study.

The number of intracytoplasmic and neuritic α-synuclein inclusions in the olfactory bulb and tract is low in the majority of cases, suggesting that α-synuclein aggregates, as visualized in current histological preparations, barely begin to explain the severity of olfactory decline. It may be hypothesized that as in other regions, olfactory alterations in PD are the result of more complicated settings resulting from several molecular deficits. In this line, changes in carbonylation and nitration have been found in the olfactory bulbs of old mice (Vaishnav et al., 2007), and increased oxidative damage has been reported in accelerated senescence-prone, short-lived (SAMP) mice (Hosokawa, 2002). Targets of oxidation in aged olfactory bulbs, as revealed by redox proteomics, are aldolase 1 and ferritin heavy chain (Vaishnav et al., 2007).

Preliminary results in our laboratory have shown increased oxidative damage, as seen with gel electrophoresis and Western blotting using malondialdehyde-lysine (MDA-Lys) and 4-hydroxinonenal-lysine (HNE) to reveal lipoxidative damage in the olfactory bulb at Braak stages 3–4 when compared with age-matched controls (Fig. 3) Therefore, increased oxidative stress and oxidative damage in the olfactory bulb and tract in PD is not the only effect of aging.

On the other hand, olfactory deficiencies may not be restricted to the olfactory bulb and tract, but rather may extend to other nuclei which process olfactory stimuli since the piriform cortex and amygdala may have crucial implications as well. In this line, LB pathology seems to be more severe in the temporal division of the piriform cortex than in the frontal division of the piriform cortex, the olfactory tubercle, and anterior part of the entorhinal cortex, at least in a restricted series of cases (Silveira-Moriyama et al., 2009).

The amygdala is involved at limbic and neocortical stages of PD-related pathology according to the instrumental classification of Braak, and it atrophies with age in PD (Bouchard et al., 2008). Interestingly, LBs and LNs in the amygdala more strongly correlate with LBs and LNs in the anterior olfactory nucleus than with those in the olfactory bulb (Sengoku et al., 2008).

Several functional studies have linked loss of olfaction and the amygdala. Olfactory stimulation activates the brain regions related with olfactory processing including the amygdaloid complex and orbitofrontal cortex; this activation is bilateral in control subjects but limited to the left hemisphere in individuals with PD (Westermann et al., 2008). Additional studies have shown that olfactory deficits correlate with atrophy of the right entorhinal cortex and right amygdala in PD (Wattendorf et al., 2009). Moreover, functional magnetic resonance imaging further supports reduced neuronal activity in the amygdala in PD (Hummel et al., 2010). Odor identification impairment in PD is associated with reduced regional metabolic rate of glucose consumption, as revealed with (18)F-fluorodeoxyglucose positron emission tomography [(18)F-FDG PET], in the cerebral cortex, amygdala, and piriform cortex (Baba et al., 2011). Finally, olfactory deficits correlate with reduced acetylcholinesterase activity in the amygdala as revealed with olfactory testing and (11)C]methyl-4-piperidinyl propionate acetylcholinesterase brain PET emission tomography in subjects with moderately severe PD (Bohnen et al., 2010).

However, it needs to be stressed that no apparent morphological abnormalities in the cholinergic system appear to be present at stages 1 and 2 of Braak, and, therefore, cholinergic denervation of the limbic cortex is probably not the only factor accounting for olfactory disorder in early pre-motor stages of PD. Morover, no LBs or LNs occur in the amygdala at stages 1, 2 and 3 of Braak. Detailed immunohistochemical studies are still needed to elucidate fine neurotransmitter deficits in the amygdala at early stages of PD.

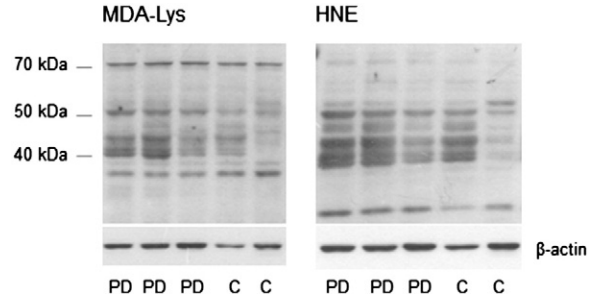

Fig. 3. Gel electrophoresis and Western blotting of the olfactory bulb in control and PD cases (stages 3–4 of Braak) processed with anti-MAD-Lys and HNE antibodies showing significant increase ($p<0.05$, Student's t-test) of lipoxidative adducts in PD compared with age-matched controls.

Sleep disorders

The molecular bases of sleep disorders are not known. Yet alterations in the pedunculopontine nucleus has been proposed as a candidate of sleep disorder (Arnulf et al., 2010; Scherfler et al., 2011). In addition, the ventral visual stream appears to be involved in visuoperceptive alterations asociated with REM disorders (Marques et al., 2010).

Hypocretin (orexin) cell loss following an anterior-to-posterior gradient has been found in the hypothalamus of PD cases with disease progression, and this finding has been proposed as a morphological and biochemical substrate of sleep alterations (Fronczek et al., 2007; Thannickal et al., 2007). However, expression levels of orexin in the CSF are variable in PD, and they are not apparently related with sleep disturbances (Compta et al., 2009). Whether orexin levels correlate with sleep attacks, and whether the action of orexin is mediated by dopamine receptors 3 (Asai et al., 2009), awaits validation.

Psychiatric symptoms

Neuropathological studies have shown that hallucinations correlate with the number of Lewy bodies in the amygdala, and frontal, temporal and parietal cortical areas in one study (Papapetropoulos et al., 2006), and in temporal lobe, claustrum and visual cortex in others (Harding et al., 2002; Yamamoto et al., 2007). Furthermore, LBs in the amygdala increase the risk of major depression in individuals with Alzheimer's disease (López et al., 2006).

Besides neuropathological observations, an imbalance between serotoninergic and dopaminergic systems, cortical cholinergic deficiency and overstimulation of mesocorticolimbic dopamine receptors have been proposed as the molecular substrates of these alterations (Birkmayer and Riederer, 1975; Frisina et al., 2009; Mayeux et al., 1986; Papapetropoulos and Mash, 2005; Perry et al., 1991; Remy et al., 2005; Wolters, 2001).

An interesting and not fully understood paradigm is the involvement of the amygdala in psychiatric symptoms in PD. Decreased responsiveness is found in the amygdala in PD in the face of fearful facial expressions, facial, prosodic and written verbal stimuli, and decision-making and facial emotion recognition (Kan et al., 2002; Yoshimura et al., 2005; Ibarretxe-Bilbao et al., 2009). Neuropathological observations have shown no apparent differences in the amygdala between depressed

and non-depressed PD cases (Frisina et al., 2009). However, depressive symptoms in PD correlate with increased serotonin transporter (Politis et al., 2010) and with a loss of dopamine and noradrenaline innervation (Delaveau et al., 2009; Remy et al., 2005) in amygdala and other limbic structures. Finally, fatigue has been associated with reduced serotonin transporter binding in the amygdala (Pavese et al., 2010).

Cognitive impairment

Morphological correlates to the cognitive deficits and abnormal behavior in PD are far from clear. Some studies have shown association between cortical LBs and cognitive impairment (Braak et al., 2005; Dickson et al., 2010; Martilla et al., 2010). Yet other studies have not confirmed this assumption (Jellinger, 2008, 2009; Libow et al., 2009; Parkkinen et al., 2008; Parkkinen et al., 2005a,b; Weisman et al., 2007), prompting the assumption that LBs per se are not causative of cognitive impairment and dementia in PD.

Associated AD pathology has been suggested as an important cofactor in the progression of cognitive impairment in PD (Jellinger, 2009). In addition, white matter hyperintensities are more frequent in PD cases with altered cognition than in cases with preserved cognitive functions (Lee et al., 2010a,b). Yet vascular abnormalities are very common in aged patients with PD (Jellinger, 2010), and we cannot rule out the possibility that white matter alterations are related to associated vascular/circulatory lesions rather than to primary lesions of PD.

Additional studies have not clarified a predictive role of LBs in the occurrence of cognitive deficits (Burke et al., 2008; Halliday et al., 2008) although LB pathology correlates with visual hallucinations when present in the medial temporal lobe and visual areas (Harding et al., 2002; Yamamoto et al., 2007). LBs in the entorhinal cortex and anterior cingulate cortex predict cognitive deficits in PD (Kövari et al., 2003). Other studies have shown that α-synuclein aggregates in limbic regions are related to dementia in PD, as well as to visual hallucinations when there is an underlying dementia (Kalaitzakis et al., 2009).

Impaired dopaminergic, cholinergic, noradrenergic and serotoninergic innervation

Cognitive and executive deficits have been related, in part, to reduced dopaminergic innervation in the nigro-striatal and mesocortical dopaminergic systems directly and indirectly compromising prefrontal cortical function via alteration of the basal ganglia (Cools et al., 2002; Cropley et al., 2008; Dagher, 2001; Dirnberger et al., 2005; Marklund et al., 2009; Monchi et al., 2007; Owen et al., 1998). [18F] FDOPA uptake is reduced in frontal association areas in later stages of PD (Moore et al., 2008). However, altered cognitive performance is not clearly related with impaired dopaminergic innervations of the cerebral cortex at early stages of the disease. PET studies with [11C] NNC112 and [18F] FDOPA have not shown significant associations between D(1) receptor density in the frontal cortex and performance at early stages of PD, in spite of a significant association between reduced [18F] FDOPA uptake in the putamen and poor performance in cognitive tests (Cropley et al., 2008). Along the same lines, attenuated dopamine release has been observed in the dorsal caudate but not in the medial prefrontal cortex in early PD patients (Sawamoto et al., 2008).

In addition to altered dopaminergic innervation, monoaminergic innervation depending on the locus ceruleus, serotoninergic innervation derived from neurons of the raphe neurons, and cholinergicic innervation provided by neurons of the nucleus basalis of Meynert are deficient in the neocortex in PD (Baloyannis et al., 2006; Bosboom et al., 2003; Hilker et al., 2005; Zarow et al., 2003). These have been proposed as concomitant factors in the pathogenesis of cognitive deficits in PD.

Regarding serotoninergic innervation, alteration of the serotonin transporter, as revealed by 123I-FP-CIT SPECT, has been observed in PD and with much more severe involvement in DLB, despite the comparable loss of striatal dopamine transporter (Roselli et al., 2010).

More specifically, cholinergic deficiencies, similar to those seen in AD, have been proposed as causative of frontal dysfunction in PD (Calabresi et al., 2006; Dubois et al., 1990). Early alteration of the cholinergic innervation of the cerebral cortex in PD, and correlation of cholinergic decline with cognitive impairment and dementia (Bohnen and Albin, 2009; 2011; Bohnen et al., 2010; Klein et al., 2010; Shimada et al., 2009), further reinforces this hypothesis.

A combination of dopaminergic and cholinergic deficiencies has been proposed as determining condition for the apperance of cognitive dysfunctions (Calabresi et al., 2006; 2007). Further details of the relationship between reduced monoaminergic and cholinergic functions, and cognitive impairment have been reviewed elsewhere (Brooks and Pavese, 2010).

Synaptic cortical pathology

Altered metabolic events at the synapses may impair synaptic function and aberrant synaptic plasticicity in PD (Hashimoto and Masliah, 2003). *tau* phosphorylation and α-synuclein phosphorylation are increased in synaptic-enriched fractions of frontal cortex homogenates in PD in the absence of LBs in the same tissue samples (Muntané et al., 2008). This indicates early α-synuclein alterations at the synapses even in cases with no cognitive impairment (Muntané et al., 2008). Recent observations have further demonstrated the presence of small abnormal aggregates of α-synuclein at the synapses (Schulz-Schaeffer, 2010; Tanji et al., 2010). These are important independent observations showing that synaptic pathology occurs in the absence of LBs and that the most common alteration in the cerebral cortex in PD is pathology at the synapses rather than the presence of LBs.

It bears stressing that increased expression of α-synuclein reduces neurotransmitter release (Nemani et al., 2010), and that abnormal α-synuclein may result in altered protein–protein interactions leading to altered synaptic function. Thus anomalous interactions have been reported between α-synuclein and Rab3a, a protein involved in synaptic vesicle trafficking, Rab5, a protein involved in dopamine endocytosis, and Rab8, a protein engaged in transport in DLBs (Dalfó et al., 2004b). Similar alterations have been reproduced in a transgenic mice model bearing the A30P α-synuclein mutation (Dalfó et al., 2004c). Altered interactions have also been suggested between altered α-synuclein and phospholipase C (PLCβ1), a signaling downstream step of metabotropic glutamate receptors in DLB (Dalfó et al., 2004a).

Impaired cortical metabolism

Cerebral glucose metabolism is reduced in the cerebral cortex in PD patients suffering from cognitive impairment (Yong et al., 2007). Limited, mainly posterior, blood flow reductions have been reported in PD cases with mild cognitive deficits assessed by rCB scintigraphic study using TC-HMPAO-SPECT (Wallin et al., 2007). Moreover, metabolic and neuroimaging observations have recently documented decreased prefrontal and parietal 18F-fluorodeoxyglycose uptake in PD cases with mild cognitive deficits (Huang et al., 2007; Huang et al., 2008). Parallel conclusions have been obtained using magnetic resonance; T1-weighed images and mean diffusitivity and fractional anisotropy values are increased in the frontal cortex in PD (Karagulle Kendi et al., 2008; Tessa et al., 2008).

Longitudinal studies have shown that idiopathic PD is accompanied by decreased metabolism in the visual association and posterior cingulate cortices; two years later, (18)F-FDG PET showed that progression of dementia in the same series of cases was associated with mixed subcortical and cortical deficits involving the mesiofrontal lobes too (Bohnen et al., 2011). Hippocampal and frontal atrophy was also reported in similar cases (Jokinen et al., 2010).

Mitochondria and energy machinery failure in the cerebral cortex

Early studies demonstrated abnormalities in complex I of the respiratory chain in the substantia nigra in sporadic PD (see Schapira 2008, for review). Later on, several genes encoding proteins relevant to maintaining mitochondrial integrity were shown to be causative of familial PD, including DJ1, PINK1, LRRK2, HtrA2 and parkin (Abou-Sleiman et al., 2006; Clark et al., 2006; Dodson and Guo, 2007; Park et al., 2006; Poole et al., 2008; Sack, 2009; Silvestri et al., 2005; Smith et al., 2005; Ved et al., 2005; Winklhofer and Haass, 2010; Yang et al., 2005).

These observations point to the possibility that mitochondrial dysfunction plays a crucial role not only in dopaminergic neurons of the substantia nigra but also in the whole brain. In this line, subunits of mitochondrial complex I are oxidatively damaged, functionally impaired and misassembled in PD (Keeney et al., 2006). Several mitochondria-associated proteins are oxidized in A30P α-synuclein transgenic mice (Poon et al., 2005).

Moreover, different parallel methodological approaches have revealed mitochondrial alterations in the neocortex in PD. Phosphorus and proton magnetic resonance spectroscopy have confirmed generalized mitochondrial dysfunction in PD (Hattingen et al., 2009). In addition, neurochemical studies in optimally preserved human post-mortem brain tissue have shown decreased brain cortex and mitochondrial O_2 uptake and reduced complex I activity in PD. This is accompanied by an increase in mitochondrial nitric oxide synthase activity, cytochrome content, expression of SOD2, mitochondrial mass, and oxidative damage in the frontal cortex in PD when compared with age-matched controls (Navarro and Boveris, 2009; Navarro et al., 2009).

An intriguing point is the observation of decreased globin α and globin β in neurons containing small α-synuclein deposits or LBs in the brain stem and amygdala in PD, and cerebral cortex in DLB (Ferrer et al., 2011a). Whether these alterations can be considered a manifestation of an anemic condition of affected neurons depends on whether globins are assembled as hemoglobin in neurons, and whether their function is related with intraneuronal O_2 transport. Current research of our laboratory is studying this intriguing question.

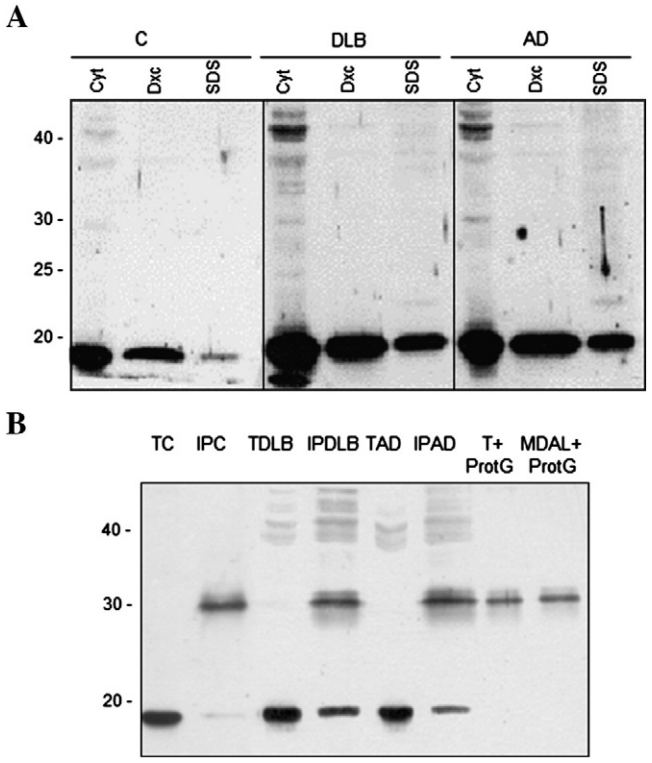

Fig. 4. A: Gel electrophoresis and Western blots of amygdala homogenates from control (C), Dementia with Lewy bodies (DLB) and Alzheimer disease with amygdala-predominant Lewy pathology (AD). Anti-α-synuclein antibody reveals a specific band of about 17 kDa (monomeric α-synuclein) in the cytosolic (Cyt), deoxycholate (Dxc) and SDS fractions in control and diseased cases. In addition, several bands of about 40 kDa are seen in the Cyt fraction in DLB and AD. MDA-Lys immunoprecipitation followed by α-synuclein blotting shows the presence of α-synuclein in immunoprecipitates of cases of Dementia with Lewy bodies (IPDLB) and Alzheimer disease with amygdala-predominant Lewy pathology (IPAD), but not in immunoprecipitates from one control (IPC). Note positive α-synuclein immunoreactivity in total homogenates (TC, TDLB and TAD). There is no specific band in the lanes containing total homogenates and protein G-sepharose without anti-synuclein antibody (T + PrtG), and anti-MDA-Lys and protein G-sepharose without sample (MDAL + ProtG).

Oxidative damage

Increased oxidative damage has been detected in the frontal cortex, in addition to that reported several years ago in the substantia nigra, in PD (Alam et al., 1997). Increased glutathione peroxidase, one of the main antioxidant enzymes inactivating hydrogen peroxide, is found in microglial cells of the gray matter and white matter in PD and DLB (Power and Blumbergs, 2009).

Increased lipoxidative damage, as seen with malondialdehyde-lysine (MDA-Lys) and 4-hydroxinonenal-lysine (HNE), and increased expression of advanced glycation end products (AGE), have been observed in the amygdala and cerebral cortex in iPD, PD and DLB (Dalfó et al., 2005; Dalfó and Ferrer, 2008). Moreover, α-synuclein is a target of oxidative damage in all these conditions (Dalfó and Ferrer, 2008). α-synuclein in amygdala-predominant LBD has abnormal solubility and forms abnormal aggregates (O'Connell et al., 1998) (Fig. 4A). MDA-Lys-modified α-synuclein is also observed in amygdala-predominant α-synucleinopathy (Fig. 4B).

Redox proteomics has been useful in identifying protein targets of oxidative damage in aged control and diseased brains (Martínez et al., 2010) (Fig. 5). In addition to α-synuclein, several key proteins are targets of oxidative damage in the frontal cortex even at very early stages of PD-related pathology, including β-synuclein and SOD2 (Dalfó and Ferrer, 2008; Dalfó et al., 2005). Other relevant proteins are also oxidatively damaged in PD: UCHL1, SOD1 and DJ-1 (Choi et al., 2004; Choi et al., 2005; Choi et al., 2006). In addition, increased oxidative damage to aldolase A, enolase 1 and glyceraldehyde dehydrogenase (GAPDH), all of them involved in glycolysis and energy metabolism, is found in the frontal cortex in pre-motor stages of PD and in established parkinsonian PD disease as well (Gómez and Ferrer, 2009). Other proteins have also been identified as lipoxidatively damaged using the malonaldehyde-Lysine marker: phosphoprotein enriched in astrocytes, SH3 domain binding glutamic acid-rich protein-like, ubiquitin-conjugating enzyme E2N-like, proteasome subunit Y and thioredoxin (unpublished observations).

It needs to be stressed that oxidative protein damage in PD, as in other neurodegenerative diseases, may also occur in age-matched controls although to a lesser extent and in a lower percentage of individuals. Thus oxidative damage of aldolase A, enolase 1 and GAPDH was also observed in a few control cases used in the study of protein damage in the frontal cortex in iPD; in contrast, these changes occurred in all iPD samples (Gómez and Ferrer, 2009).

Oxidative damage in cerebral cortex has also been reported in familial cases bearing *LRRK2* mutations in the absence of apparent cognitive impairment and in the absence of LBs in cerebral cortex (Gomez and Ferrer, 2010). This further supports the concept that molecular changes occur in PD neocortex in spite of apparent lack of cognitive deficits, and that the cerebral cortex is affected in PD independently of its being associated (or not) with the presence of LBs.

Increased oxidative damage in peripheral blood correlates with severity of PD (Chen et al., 2009), but this alteration does not necessarily represent worsening of cognitive functions.

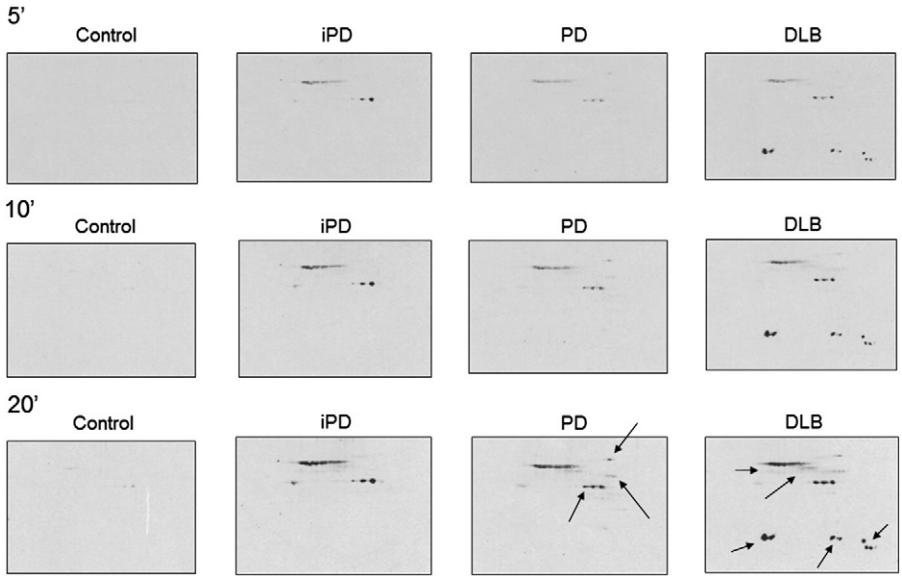

Fig. 5. Bi-dimensional gel electrophoresis and Western blotting using MDA-Lys antibodies in cerebral cortex (area 8) homogenates from control, iPD, PD and DLB cases at various times (5, 10 and 20 min) following antibody incubation. Dots (arrows) represent MDA-Lys-modified proteins, the number and intensity of which increase from iPD to DLB. Note that no spots are seen in this particular control case.

mRNA profiling. Altered mRNA splicing and altered ribosomal protein expression?

The use of different 'omics' is becoming useful in the study of pathogenesis and the discovery of putative biomarkers in PD (Caudle et al., 2010; Mellick et al., 2010).

Transcriptional analyses have shown altered transcription in multiple brain regions in PD (Bossers et al., 2009; Zhang et al., 2005). Yet most studies are limited to the substantia nigra and have shown dysregulation of genes involved in PD pathogenesis (PARK family members), dopamine metabolism, mitochondrial metabolism, proteolysis, kinase pathways, synapse regulation, and cell death and survival, among others (Duke et al., 2006; Grundblatt et al., 2004; Hauser et al., 2005; Lesnick et al., 2007; Mandel et al., 2005; Miller et al., 2006; Simunovic et al., 2009). Further evidence of impaired mitochondrial gene expression in the striatum has been reported in mouse models of PD (Chin et al., 2008; Smith, 2009).

Although studies geared to improving understanding of gender differences in gene expression in the neocortex in PD have not been reported, preliminary results in our laboratory suggest that RNA dysregulation differs in males and females once correction is made for age and disease stage (unpublished observations).

Gene expression studies in the cerebral cortex in PD are scanty. Dysregulated gene expression has been reported in the posterior cingulate cortex in PD, and abnormal gene expression increases in PD cases with dementia (Stamper et al., 2008). Variegated genes are affected on the basis of a determined fold-increase or decrease value rather than on the identification of clusters of genes belonging to specific metabolic pathways.

An interesting point is the observation of down-regulation of numerous genes involved in mRNA splicing, thereby implicating alterations in the mRNA processing in the pathogenesis of dementia in PD (Stamper et al., 2008).

Preliminary observations have also shown alterations in the expression of several genes encoding ribosomal proteins. The ribosome is composed of mRNA and ribosomal proteins that confer the tertiary structure to the ribosome. Eukaryotic initiation factors (eIF) are proteins involved in the initiation phase of translation by recognizing and recruiting ribosomal subunits to form the active 80S ribosome. Eukaryotic elongation factors eEF-1 and eEF2 mediate the entry of the new amynoacyl tRNA (charged tRNA) into a free site of the active ribosome at the end of the peptide chain. Termination of the polypeptide occurs when the A site of the ribosome recognizes a stop codon. Peptides and proteins are delivered by releasing factors which recognize non-sense codons (Cox and Philipis, 2007). Our mRNA studies have shown up-regulation of several ribosomal protein mRNAs in the frontal cortex, area 8, at stages 3 and 4 of Braak, whereas several ribosomal protein mRNAs are down-regulated in the same region at stages 5 and 6. Alteration in the expression of ribosomal protein mRNAs may result in altered expression of protein subunits which may impair protein binding to ribosomal messenger RNA and, therefore, may alter the tertiary structure of the ribosomal complex. Moreover, eEF-1 mRNA is also up-regulated in the frontal cortex at middle stages of PD.

Together, these observations point to the splicitome and ribosome as additional vulnerable molecular mRNA translation mechanisms in PD.

Altered microRNA expression

In a different setting, we recently reported down-regulation of two microRNAs, miR-34b and miR-34c, in the amygdala and frontal cortex in PD. Down-regulation of miR-34b or miR-34c in differentiated SH-SY5Y dopaminergic neuronal cells resulted in a moderate decrease in cell viability that was accompanied by altered mitochondrial function and dynamics, oxidative stress, and a decrease in total cellular ATP content. This was accompanied by decreased DJ1 and parkin expression. These findings support the notion that deregulation of miR-34b/c in PD triggers downstream transcriptome alterations underlying mitochondrial dysfunction and down-regulation of DJ1 and parkin in PD (Miñones-Moyano et al., 2011). Importantly, down-regulation of miR-34b/c in the amygdala was detected in pre-motor stages (stages 1–3) of the disease, and thus in cases which did not receive any PD-related treatment during life (Miñones-Moyano et al., 2011). Since these alterations are also found in the substantia nigra (and to lesser extent in the cerebellum), it is feasible that the phenomenon is widely distributed in PD brain (Miñones-Moyano et al., 2011).

Altered protein expression in neocortex

Proteomics in PD is mainly focused on the substantia nigra (Basso et al., 2004; Fasano and Lopiano, 2008; Kitsou et al., 2008; Werner et al., 2008). Yet differential protein expression in the pioneering analyses differs from one study to the other, thus suggesting limitations

or pitfalls in the methods employed. More precise results have been obtained with the utilization of subcellular fractionation. In this line, several proteins have been identified after isolation of midbrain and cortical LBs from LBD cases (Leverenz et al., 2007; Schults, 2006; Wakabayashi et al., 2007; Xia et al., 2008; Zhou et al., 2004), and of neuromelanin granules (Tribl et al., 2005).

Mitochondrial proteomics has also been particularly useful to complement the abundance of data indicating the cumulative defects of mitochondria in PD (Pienaar et al., 2010). In addition to preliminary studies on total homogenates of the human substantia nigra (Basso et al., 2004; Ferrer et al., 2007; Werner et al., 2008), proteomics in rodent (Chin et al., 2008; Jin et al., 2006; Palacino et al., 2004; Periquet et al., 2005) as well as in *Drosophila* (Xun et al., 2007, 2008, 2009) models of PD has lent support to the notion of altered expression of multiple mitochondria-related proteins. Mortalin (mthsp70, GRP75) that functions as a mitochondrial chaperone was observed to be reduced in PD substantia nigra (Jin et al., 2006).

Research on protein expression in the neocortex in LBDs is more limited (Caudle et al., 2010; Pan et al., 2007; Shi et al., 2008). Several hundred proteins are dysregulated in the cerebral cortex in PD (Caudle et al., 2010; Shi et al., 2008). Preliminary proteomic studies using bi-dimensional gel electrophoresis and mass spectrometry in our laboratory have shown altered expression of several proteins in the frontal cortex at pre-motor stages of PD including ATP synthase α-subunit isoform b, glyceraldehyde 3-phosphate dehydrogenase, prohibitin, porin, carbonic anhydrase II, vacuolar proton ATPase, acyl-CoA thioester hydrolase, elongation factor Tu, ferritin heavy chain, ferritin light subunit and αB-crystallin, among others (unpublished observations). These and other reported data have to be interpreted cautiously until verification in other series of experiments and with additional samples. Proteomics using bi-dimensional gels in post-mortem brain samples is still subject to validation with other methods (Crecelius et al., 2008). However, in one of these studies, mortalin was also found to be decreased with disease progression in the cerebral cortex in PD (Shi et al., 2008), corroborating earlier observations of mortalin alteration in the substantia nigra in PD. Interestingly, glutathione S-transferase pi, involved in the regulation of oxidative stress, is also dysregulated in the cerebral cortex with disease progression in PD (Shi et al., 2009). High throughput proteomics, with the power of identifying simultaneously thousands of proteins, is expected to enhance discovery of biomarkers and therapeutic targets and unravel novel pathways contributing to disease pathogenesis.

Lastly, redox proteomics, as reported above, followed by functional studies and analyses of enzymatic activities of specific oxidized or nitrated proteins, is the complementary method of choice for detecting post-transcriptional modifications of proteins. Studies of other post-translational modifications, such as phosphorylation and glycation of proteins other than α-synuclein and PD-related proteins in the PD cerebral cortex, are at the phase of a promising beginning.

Altered lipid composition of cortical membranes: lipid rafts

Abnormal lipid composition occurs in the frontal cortex at very early stages of PD-related pathology with significantly increased expression levels of the highly peroxidizable docosahexanoic acid (DHA), and increased peroxidability index (Dalfó et al., 2005). Importantly, altered lipid composition is particularly marked in lipid rafts, membrane specializations crucial for protein interactions and traffic. Dramatic reductions are seen in the n−3 and n−6 long chain polyunsaturated fatty acid (LCPUFA) content, mainly docosahexaenoic acid (22:6−n3) and arachidonic acid (20:4n−6), as well as increased medium- and long-chain saturated fatty acids (16:0 and 18:0) when compared with control brains, thus leading to increased membrane viscosity and, probably, to increased oxidative stress (Fabelo et al., 2011).

The term ‘exahusted neuron’ was employed in Alzheimer's disease to designate a combination of metabolic events leading to persistently impaired energy production accompanied by increased energy demands that may be detected at very early stages of disease even in cases without overt clinical symptoms of cognitive impairment and dementia (Ferrer, 2009b). A similar scenario also occurs, albeit with different targets (different primary involvement of respiratory chain complexes, different lipoxidative and glycoxidative damage, different alteration of membrane lipid composition), in PD (Naudi et al., 2011). A further example of metabolic failure with impairment of energy production involving oxidative damage of mitochondria and glycolytic enzymes is found in the axonopathic mouse model of adrenoleukodystrophy (Galino et al., 2011). Of note, this disease is directly caused by the accumulation of saturated very long chain fatty acids and the ensuing oxidative damage this excess generates in the cels (Ferrer et al., 2010; Fourcade et al., 2008; López-Erauskin et al., 2011).

Removal of altered proteins and intracellular debris: UPS and autophagia

Removal of altered proteins and intracellular debris is carried out by several mechanisms including cytosolic proteolysis, activation of the ubiquitin–proteasome system (UPS) and autophagia. Misfolded proteins or un-assembled subunits of larger protein complexes and retro-translocated proteins from the endoplasmic reticulum are subject to rapid proteasomal degradation. The ubiquitin–proteasome pathway is initiated by the conjugation of ubiquitin to the substrate leading to poly-ubiquitination of the substrate. The conjugation of the target protein to a chain of ubiquitin molecules is recognized by the 26S proteasome which is composed of the 20S proteasome and the 19S or the 11S activator, PA28αβ complex. Three catalytic β subunits of the 20S proteasome can be replaced by homologous proteins LMP2, LMP7 and MECL1, thus forming the so-called immunoproteasome. The 20S proteasome has three main peptidase activities: chymotrypsin-like, trypsin-like and peptidylglutamyl peptide (PGPH) hydrolyzing activities (Botchler et al., 1999; Glickman and Ciechanover, 2002; Herschko, 1998).

Mutations in certain ligases and hydrolases linked to the UPS are involved in subgroups of familial cases of PD; one of these ligases is parkin (Kitada et al., 1998); one of these hydrolases is UCHL1 (Leroy et al., 1998). This suggests that impaired protesomal function plays a role in the pathogenesis of familial PD. The expression levels of UCHL1 are also reduced in the substantia nigra in sporadic PD and DLB, and in the cerebral cortex in DLB (Barrachina et al., 2006). Reduction of UCHL1 expression also occurs in other brain region regions in PD (Fig. 6A).

Whether the UPS is involved in the pathogenesis of sporadic PD has been the subject of multiple studies in human and experimental models, as well as being a source of controversy (Lim, 2007). Just to summarize a few examples of differences of oppinion related to human post-mortem brain of sporadic PD, abnormal function of the UPS has been been reported in some studies (McNaught and Jenner, 2001; McNaught et al., 2002, 2003), but this observation has not been corroborated in others (Tofaris et al., 2003).

Our first analyses in α-synuclein transgenic mice and in cell cultures, as models of PD, were consistent with normal function of the UPS (Martìn-Clemente et al., 2004). We have now examined, by gel electrophoresis and Western blotting, the expression levels of several components of the UPS in the amygdala in cases of iPD and PD compared with age-matched controls. The expression of 19S, PA28α and LMP2 was significantly increased in iPD and PD when compared with controls, whereas increases in LMP7 and MECL-1 were only identified in PD when compared with controls (Fig. 6A). Regarding protelytic activities of the UPS, no modifications in trypsin-like activity were detected in iPD and PD but decreased chymotrypsin-like activity was observed in iPD, and decreased PGPH activity in PD when compared with controls (Fig. 6B). We do not know at present the reasons for the abnormal regulation of UPS proteins in PD, particularly in relation to increased protein expression of several subunits. As previously indicated,

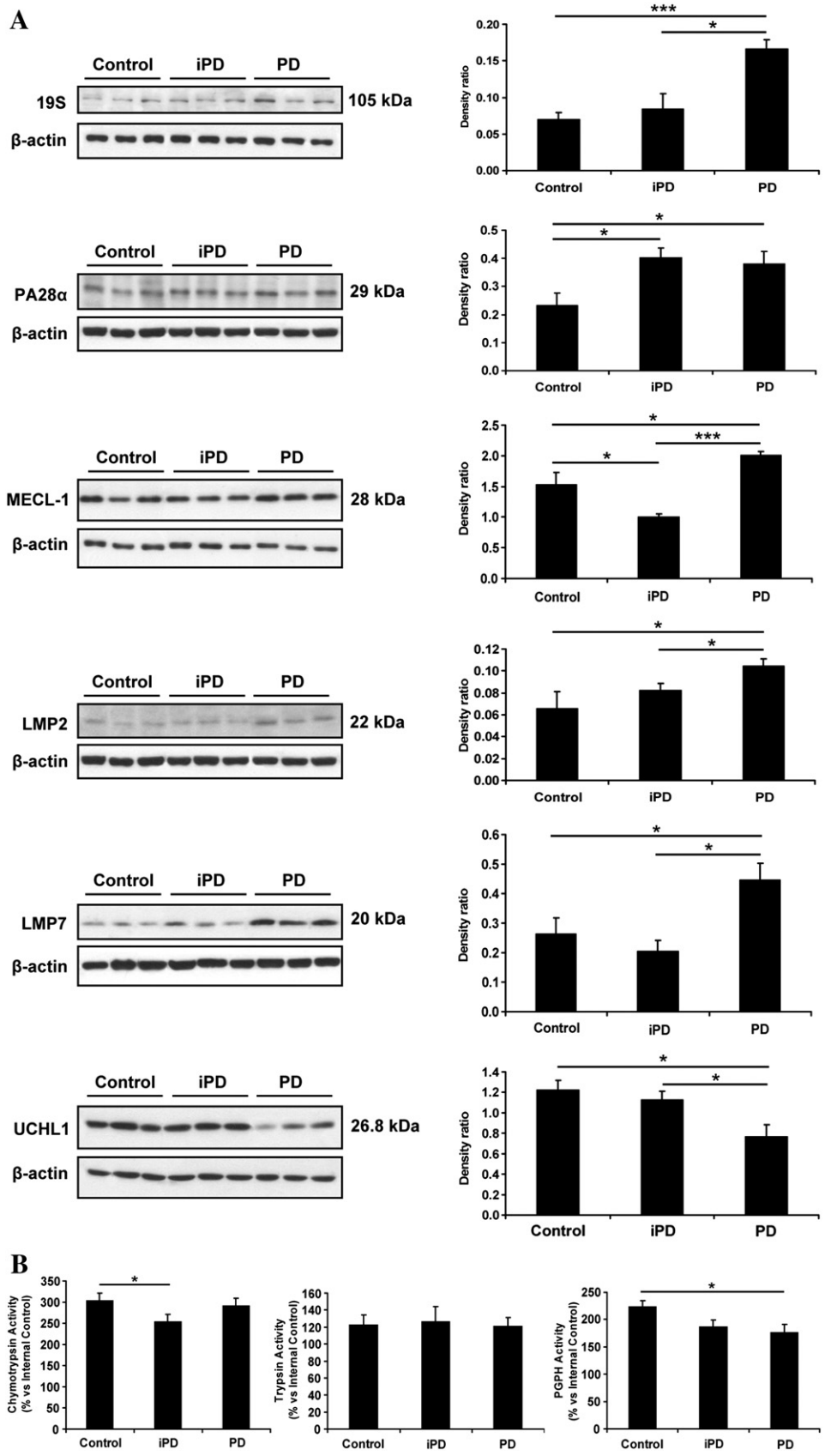

Fig. 6. A: Gel electrophoresis and Western blotting of total amygdala homogenates using antibodies against different subunits of the UPS. Results show increased protein expression of 19S, PA28α, and LMP2 in iPD and PD, and of MECL-1 and LMP7 in PD when compared with controls. UCHL1 expression is reduced. Densitometric quantification of 19S, PA28α, MECL-1, LMP2, LMP7 and UCHL-1 levels respect to β-actin. All values are shown as the mean ± SEM of 5 pacients per group. *$p<0.05$ and ***$p<0.001$ (Student's t-test). B: Chymotrypsine-like, trypsin-like and peptidylglutamyl peptide (PGPH) activities in the total amygdala in control (n = 5), iPD (n = 4) and PD cases (n = 5). Data are represented as the mean ± SEM. * $p<0.05$ (Student's t-test).

some UPS-related proteins such as UCHL1 and proteasome subunit Y are oxidatively damaged in PD, and this phenomenon is currently associated with loss of function (Cabiscol and Ros, 2006). Compensation by other components to preserve normal function can be postulated as an operative hypothesis for future work. Yet the compensatory process, if it exists, appears to be less than optimal, as manifested by the altered performance of catalytic subunits.

The expression levels of chaperone-mediated autophagy proteins LAMP2A and hsc70 are reduced in the amygdala (and substantia nigra) in advanced PD when compared with controls, and LBs in these regions contain autophagy-related proteins (Alvarez-Erviti et al., 2010). These findings lend support to the notion of impaired autophagy in PD brains as suggested by numerous in vitro and in vivo studies in several models.

Glial cell pathology in neocortex

Glial reactions in toxic-induced and transgenic models of PD, and in the substantia nigra in PD have a role in the pathogenesis of dopaminergic damage (Chung et al., 2010; Halliday and Stevens, 2011; McGeer and McGeer, 2008; Yokoyama et al., 2011). Interestingly, astroglial reactions seem to be subjected to gender differences in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP)-induced model of PD in mice (Ciesielska et al., 2009).

Several factors with antagonistic consequences converge in the inflammatory response. On the one hand, microglial cells produce pro-inflammatory and anti-inflammatory cytokines which perpetuate neuronal damage (Roodveldt et al., 2008). On the other hand, astrocytes protect dopaminergic neurons through increased levels of glutathione peroxidase (Ishida et al., 2006), by activating the Nurr1/CoREST pathway (Saijo et al., 2009), by removing toxic molecules from the extracellular space and through the release of throfic factors (Rappold and Tieu, 2010). In addition, DJ-1 in astrocytes modulates the innate immunity signaling (Cornejo Castro et al., 2010) and confers neuroprotection to neighboring neurons (Mullett and Hinkle, 2011).

The role of α-synuclein in this process is still obscure. However, transfer of α-synuclein from neuron to astroglia causes changes in the gene expression profile of astrocytes and promotes the induction of cytokines (Lee et al., 2010a,b). Moreover, selective expression of A53T mutant α-synuclein in astrocytes induces neurodegenration in transgenic mice (Gu et al., 2010). Finally, mitochondrial alterations have been observed in astrocytes of the mesencephalon but not of the cerebral cortex in genetic mouse models of PD (Schmidt et al., 2011). Such alterations are associated with reduced Ca^{2+} storage, altered oxidative stress responses and reduced trophic factor activity on co-cultured neurons (Schmidt et al., 2011).

Little is known about glial reactions in the neocortex in PD. α-synuclein in astrocytes has been reported in the amygdala, thalamus, septum, striatum, claustrum and cerebral cortex in PD, probably as a result of α-synuclein leakage from projection neurons to these areas (Braak et al., 2007). It is clear that further studies are needed to elucidate the role of microglia and astrocytes in relation with cognitive impairment in PD.

α-Synuclein pathology without LBs in the cerebral cortex in the elderly

As previously indicated, the term iPD was introduced to designate the discovery on post-mortem neuropathological examination of LBs in selected brain regions in individuals without any clinical evidence of parkinsonism (Jellinger, 2004; Saito et al., 2004). Further studies were focused on the presence of LBs in the absence of clinical symptoms in the elderly (Markesbery et al., 2009), thus promoting the notion of a gradient between normal individuals without LBs, subclinical old people with LBs mainly located in the brainstem, and individuals affected by PD or DLB.

Biochemical studies of α-synuclein in apparent controls (brain samples from individuals with no evidence of neurological symptoms and lacking protein inclusions and protein deposits on neuropathological examination) processed in parallel with samples from cases with LBs have shown interesting individual variations among the control population. Preliminary observations have shown oxidized α-synuclein in a subset of control individuals with no apparent α-synuclein pathology based on the lack of intracellular α-synuclein inclusions (Dalfó and Ferrer, 2008). Additional studies have corroborated the presence of lipoxidized α-synuclein, as revealed by MDA-Lys immunoprecipitation and α-synuclein immunoblotting, in the amygdala of 30% of control individuals older than 65 years. LBs, LNs and other intracellular α-synuclein aggregates were not found in these cases, even using formic acid pre-treatment for antigen enhancement (Fig. 7). No similar studies are available in other brain regions.

Obviously, these are very specific observations and no general conclusions can be drawn at this point. Moreover, we do not know whether control individuals would have developed LBs if they had survived for a longer time. Yet α-synuclein lipoxidative damage without LBs is also found in the neocortex of cases with sporadic iPD and PD (Dalfó and Ferrer, 2008; Ferrer, 2009a,b) and in the cortex of cases with inherited PD due to mutations in *LRRK2* (Gomez and Ferrer, 2010). Therefore, we can hypothesize a scenario in which α-synuclein is oxidatively damaged with aging in a subgroup of individuals, and

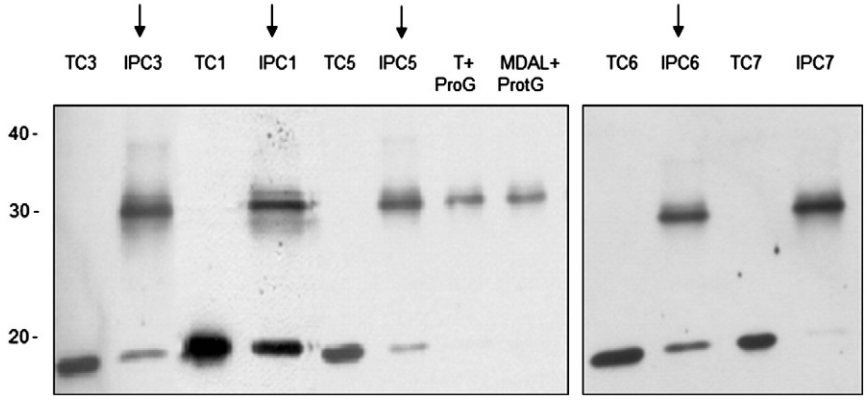

Fig. 7. MDA-Lys immunoprecipitation followed by α-synuclein blotting shows the presence of α-synuclein in immunoprecipitates of four cases (IPC1, IPC3, IPC5 and IPC6: arrows), but not in another control (IPC7). Positive α-synuclein immunoreactivity is found in total homogenates (TC) in every case. The specific reaction is negative in the lanes containing total homogenates and protein G-sepharose without anti-synuclein antibody (T + ProtG), and anti-MDA-Lys and protein G-sepharose without sample (MDAL + ProtG). In spite of the abundance in the number of cases with lipoxidized synuclein, these represent about 30% of cases in control individuals older than 65 years (4 of 15 cases).

that this modification impairs proper α-synuclein function and facilitates LBD pathology in a reduced number of cases.

Other modifications of α-synuclein in normal aging are less well documented. Phosphorylated α-synuclein at Ser129 and truncated α-synuclein have been observed in total homogenates of the substantia nigra in a number of aged control individuals (unpublished observations). Whether these findings have any mechanism in common with the observation of phosphorylated α-synuclein at Ser129 in synaptic-enriched fractions of the neocortex in iPD, PD and DLB, and in AD stage III onwards (Muntané et al., 2008) is a stimulating question.

Concluding comments

PD can no longer be considered as a motor disease but rather as a systemic disorder involving the central, autonomic and peripheral nervous systems. Moreover, PD is not just a disease with abnormal α-synuclein accumulation but rather a generalized disease in which α-synuclein is one of the players but not the only factor accounting for the whole complexity of molecular defects involving variegated metabolic pathways. Mitochondria and energy metabolism impairment, abnormal protein synthesis and post-translational protein modifications, defects of the mechanisms involved in the removal of altered proteins and cellular debris, and alterations in the composition of cell membranes are best considered as the scenario of a multi-subcellular failure. Moreover, mitochondrial abnormalities, altered lipid composition and increased oxidative damage of proteins involved in cytoskeleton, neurotransmission, mitochondrial function and energy metabolism occur at early, pre-motor stages of PD and persist with disease progression (Ferrer, 2011; Ferrer et al., 2011b; Tang et al., 2010). Moreover, altered synaptic function and impaired innervations affecting different neurotransmitters, as occur in the cerebral cortex in addition to the nigrostriatal system, alter the ecosystem of neurons as social cells which depend on interaction with other neurons through complex afferencies and efferencies. Importantly, concurrence of epigenetic dysregulation, altered transcription and translation, post-translational protein modifications, and alterations in lipid composition are difficult to reconcile with a reductionistic scenario of a single causative cascade of events leading to non-motor symptoms in PD.

Molecular neurochemical abnormalities outside the nigrostriatal system occur at early stages of the disease, at the so-called incidental or pre-motor stages of PD pathology, and they involve structures in which there is no evidence of classical neuropathological alterations (i.e., LBs and LNs in the neocortex and amygdala), thereby indicating that multiple subcellular defects occur very early on in PD.

Regarding therapeutical implications, the evidence of early and complex molecular defects in several regions of the nervous system highlights the importance of considering early, combined and specific therapeutic strategies geared to delaying, from the very beginning, disease progression. Therapeutic management of non-motor symptoms in PD is, however, out of the scope of the present review.

Finally, this review also brings to light the fact that the present state of knowledge concerning PD is momentary and fragmented, and remains very limited. Multiple pieces of the extremely complex puzzle are still missing, and comprehensive multidisciplinary and multimethodological studies are still needed to unveil the pathogenic mechanisms of non-motor alterations in PD.

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No relevant data.

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