Molecular Changes in the Postmortem Parkinsonian Brain

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Abstract

Despite considerable research efforts, the cellular and molecular mechanisms involved in the initiation and progression of Parkinson's disease (PD) are still unknown. As a consequence, no treatment that slows down or stops the progression of the disease is currently available. In an effort better to understand the molecular pathogenesis of this disease, we review here the biochemical changes that have been documented through the observation and the analysis of postmortem PD brains.

Introduction

Parkinson disease (PD) is a progressive neurodegenerative illness of the human nervous system afflicting more than 1% of people over the age of 65 and more than 4% of the population by the age of 85 (de Rijk *et al.* 2000). The diagnosis of PD depends upon the presence of motor deficits that in turn are predominantly the consequence of loss of dopaminergic neurons of the substantia nigra (SN). Non-motor symptoms may develop prior to motor deficits, but more frequently appear in the more advanced stages and are due to loss of both dopaminergic and non-dopaminergic neuronal pathways (Chaudhuri *et al.* 2006).

Despite significant research efforts undertaken to understand PD, available treatments are only symptomatic and do not affect the progression of the disease. Several reasons have been proposed to explain this failure, in particular the fact that research for effective treatments is hampered by lack of knowledge on the pathogenetic processes explaining this disease(Stanzione and Tropepi 2011). Indeed, while existing cellular and animal models are important for our understanding of the apparent pathogenesis of PD, paradigms that reflect the progressive nature of the illness and its complexity in terms of the extent of pathology and underlying biochemical changes are also lacking. Consequently, the progress in the development of approaches that stop or slow the disease progression is very low(Duty and Jenner 2011).

PD is a pathology affecting only humans. For this reason we believe that the study of the human brain is a prerequisite for understanding this disorder. Here we review the molecular changes observed through the analysis of the human postmortem PD brains. We will address here the changes in protein expression, excluding RNA expression data (reviewed elsewhere(Cooper-Knock *et al.* 2012)) and discuss changes in PD brain only.

Neurotransmitters and neurotrophic factors

Neurotransmitters, receptors and transporters

Cell loss is observed in PD in several brain areas. While dopaminergic cell loss is believed to be responsible for the motor alterations in the disease, glutamatergic, cholinergic, tryptaminergic, GABAergic, noradrenergic and adrenergic neurons are also affected during the progression of the pathology(Braak and Braak 2000) (Table 1). Levels of tyrosine hydroxylase (TH), the rate limiting enzyme in dopamine synthesis, dopamine transporters (DAT) and vesicular monoamine transporter 2(Thibaut *et al.* 1995) (VMAT2) are severely reduced in the SN of PD patients(Kastner *et al.* 1993). In dopaminergic neurons, increased levels of neuromelanin were reported, suggesting increased oxidation of dopamine(Halliday *et al.* 2005). Accordingly, the content of the oxidized metabolites of dopamine, notably 5-S-Cysteinyl-Dopamine, 5-S-Cysteinyl-DOPA and 5-S-Cysteinyl-DOPAC(Spencer *et al.* 1998) as well as NADH quinone oxidoreductase(van Muiswinkel *et al.* 2004) (NQO1), an enzyme that detoxifies dopamine quinone, are also increased.

The loss of dopaminergic neurons projecting fibers in the striatum induces a strong decrease in TH, DAT and VMAT2 levels in the caudate nucleus and the putamen(Wills *et al.* 2010; Miller *et al.* 1999; Ryoo *et al.* 1998; Güzey *et al.* 2012); while dopamine levels and its catabolites DOPAC and HVA are severely impaired in caudate nucleus, putamen and nucleus accumbens(Gerlach *et al.* 1996). Nevertheless, dopamine receptor 1(Mattila *et al.* 2001; Piggott *et al.* 1999; Griffiths *et al.* 1994) (D1R) and dopamine receptor 3(Piggott *et al.* 1999) (D3R) densities are not affected by the loss of dopaminergic fibers, while its effect on dopamine receptor 2 (D2R) is unclear(Varani *et al.* 2010; Ahlskog *et al.* 1991; Piggott *et al.* 1999; Griffiths *et al.* 1994).

The progression of the pathology also severely impacts the cholinergic system. Indeed, choline acetyltransferase, which catalyzes acetylcholine (Ach) production, is reduced in

several brain areas including the hippocampus, thalamus, sub-thalamic nuclei and frontal cortex(Rinne *et al.* 1989; Xuereb *et al.* 1990; Gotti *et al.* 2006; Mattila *et al.* 2001) with simultaneous reduction of the activity of acetylcholine esterase(Xuereb *et al.* 1990). The distribution and content of Ach receptors (AchR) is also changed. Global density of AchR is increased in the globus pallidus(Griffiths *et al.* 1990) and decreased in the striatum(Gotti *et al.* 2006) where nicotinic AchR density(Court *et al.* 2000), more particularly α4-, α6-, β2- and β3-subunits(Gotti *et al.* 2006), is also reduced. Decreased levels of α4- and α7-subunits were also observed in cortical regions(Burghaus *et al.* 2003; Banerjee *et al.* 2000). For the muscarinic receptors, contradictory results were observed in the putamen(Griffiths *et al.* 1994; Ahlskog *et al.* 1991) while increased density of M2 muscarinic receptor was reported in cortical structures(Rinne *et al.* 1989).

The GABAergic system is affected in PD with increased and decreased levels reported in the striatum and the thalamus, respectively(Gerlach *et al.* 1996). GABA receptor density is also decreased in the SN of PD patients(Lloyd *et al.* 1977), and GABA A receptor ($GABA_AR$) reduced in the striatum(Griffiths *et al.* 1990). This occurs in parallel with changes in glutamatergic system. Whereas glutamate levels are not modified in several brain structures implicated in the pathology, levels of the glutamate metabolite glutamine are significantly elevated in the thalamus, the globus pallidus and the caudate nucleus(Gerlach *et al.* 1996). Interestingly, density of NMDA receptor(Gerlach *et al.* 1996) and levels of metabotropic glutamate receptor 5 (mGluR5) and its downstream regulator β-arrestin(Price *et al.* 2010) were decreased in the caudate nucleus. Finally, several other systems are also dysregulated in PD since abnormal levels and/or densities of adenosine 2A(Villar-Menéndez *et al.* 2014; Varani *et al.* 2010), angiotensin II(Allen *et al.* 1992), glycine(de Montis *et al.* 1982), neurotensin(Uhl *et al.* 1986), somatostatin(Uhl *et al.* 1986), μ- and κ-opiate(Uhl *et al.* 1986) receptors have been reported.

Neurotrophic factors

Neurotrophic factors are important in the maintenance of neuronal cell survival. Several studies demonstrated dysregulation of these factors in PD (Table 1). Glial cell-derived neurotrophic factor (GDNF) levels, the prototypical neurotrophic factor for dopaminergic neurons, are decreased in the SN of PD patients(Mogi *et al.* 2001; Chauhan *et al.* 2001), as well as one of its receptor, Ret(Decressac *et al.* 2012). Brain-derived neurotrophic factor (BDNF), another neurotrophic factor essential for neuronal cell survival, is underexpressed(Mogi *et al.* 1999; Imamura *et al.* 2005; Parain *et al.* 1999; Chauhan *et al.* 2001). Epidermal growth factor (EGF) and its receptors levels are also modified(Mogi *et al.* 1994a; Iwakura *et al.* 2005; Depboylu *et al.* 2012). Transforming growth factor α (TGFα)(Mogi *et al.* 1995) and β1 (TGFβ1)(Mogi *et al.* 1995) levels are increased in PD brains, while nerve growth factor (NGF)(Mogi *et al.* 1999), ciliary neurotrophic factor (CNTF)(Chauhan *et al.* 2001) and basic fibroblast growth factor (bFGF)(Tooyama *et al.* 1994) are decreased. Neurotrophin-3, -4(Knott *et al.* 2002; Chauhan *et al.* 2001), heparin-binding EGF-like growth factor (HB-EGF)(Iwakura *et al.* 2005), and corticotropin releasing hormone (CRH)(Hoogendijk *et al.* 1998) expression is not affected in the pathology.

Lewy bodies and PD linked genes

Lewy bodies

Another hallmark of PD is the presence of intracytoplasmic fibrillar aggregates possessing a dense core and a peripheral halo forming Lewy bodies. Since excellent reviews detailing their composition were published(Wakabayashi *et al.* 2013), this issue will not be discussed in details in this review.

Postmortem studies have demonstrated that Lewy pathology progressively and gradually involves greater parts of Parkisonian brain. This progressive characteristic had been used to classify the pathology in several stages. The first lesions appears in stage 1 in the olfactory bulb and the dorsal nucleus of the vagal nerve. In stage 2, lesions progress toward the locus coeruleus and the caudal raphe nuclei. The lesions then continue their ascending path to reach the amygdala, the pedulopontine nuclei and the pars compacta of the substantia nigra. At stage 4, 5 and 6, the lesion continues its progression upward and reaches the mesocortical and cortical areas (for more details, see (Braak *et al.* 2003)).

This apparent ascending progression of the disease, combined with the observation that embryonic neuronal grafts transplanted into PD patients also contained Lewy pathology(Li *et al.* 2008), gave rise to the prion-like hypothesis, which states that PD pathology can be propagated to neighbouring cells. α-synuclein, one of the main constituent of Lewy bodies(Wakabayashi *et al.* 2013), represents one candidate that could eventually spread the pathology since it has the potency to be released from and uptaken by neurons(Steiner *et al.* 2011; Chauhan and Jeans 2015). This phenomenon is of particular interest since α-synuclein has been found mutated in some familial forms of PD(Polymeropoulos *et al.* 1997).

PD-linked genes and their interactome

Genetic studies have shown that 5-10% of PD patients suffer from a monogenic heritable form of the disease. Alterations of their expression has also been linked to idiopathic PD (Table 2).

α-synuclein

α-synuclein is of particular interest in respect with PD for mainly two reasons: as the first gene reported to contain specific genetic aberration linked to PD(Polymeropoulos *et al.* 1997),

and as one of the main component of Lewy bodies(Wakabayashi *et al.* 2013), reflecting its propensity to aggregate. Interestingly, the analysis of sporadic PD brains demonstrated that both soluble and insoluble α-synuclein levels are abnormally high in several brain structures(Wills *et al.* 2010), and at the intracellular level in mitochondria(Devi *et al.* 2008). According to Desplats(Desplats *et al.* 2011) et al., this overexpression of α-synuclein in PD brain could be the result of hypomethylation. Particularly, they observed that DNA methyltransferase 1 (DNMT1), which controls the methylation status of α-synuclein, was sequestered into the cytoplasm and thus decreased nuclear levels in PD.

In the PD brain, increased levels of α-synuclein modified through oxidation(Shamoto-Nagai *et al.* 2007), nitration(Giasson *et al.* 2000) or cleavage(Dufty *et al.* 2007) were also observed. This increase in cleaved α-synuclein could be the result of increased expression of matrix metalloprotease-3 (MMP3)(Choi *et al.* 2011). Increased levels of α-synuclein phosphorylated at S129 were also detected in PD brain(Mahul-Mellier *et al.* 2014), possibly the consequence of decreased levels of the SMG1 phosphatidylinositol 3-kinase related kinase(Henderson-Smith *et al.* 2013). Note that G-protein-coupled receptor kinase 5 (GRK5) expression, a protein that phosphorylates α-synuclein at S129, remained unchanged in PD brain(Arawaka *et al.* 2006). Finally, in the SN of PD patients, the α-synuclein dimer/monomer ratio is increased(Sharon *et al.* 2003). This observation could be, at least in part, due to increased levels of tissue transglutaminase in dopaminergic neurons of the SN of PD patients(Wilhelmus *et al.* 2011b; Citron *et al.* 2002), which had been shown to catalyze the formation of α-synuclein crosslinks(Andringa *et al.* 2004).

Parkin

Mutations inducing loss of function of the ubiquitin E3 ligase parkin are the most common known cause of young-onset familial PD(Dawson and Dawson 2010). Like α-synuclein,

parkin was found in Lewy bodies(Schlossmacher *et al.* 2002). In sporadic PD brains, while total parkin levels remained unchanged(Rubio de la Torre *et al.* 2009; LaVoie *et al.* 2005; Wills *et al.* 2010), its aggregated form was increased(LaVoie *et al.* 2005), explaining the observed reduction of its soluble form(Lonskaya *et al.* 2013). The loss of function due to parkin mutations in familial PD is paralleled in sporadic PD by a decrease in parkin availability and thus, activity. Since parkin functions as an E3 ubiquitin ligase to promote the degradation of its substrates via the proteasome, increased levels of parkin substrates should be observed in sporadic PD brain. Consistent with this hypothesis, the parkin substrates aminoacyl-tRNA synthetase-interacting multifunctional protein type 2(Imam *et al.* 2011; Ko *et al.* 2010) (AIMP2), also called Jtv1, far upstream element-binding protein-1(Imam *et al.* 2011; Ko *et al.* 2010) (FBP-1), parkin interacting substrate(Shin *et al.* 2011) (PARIS), programmed cell death-2 isoform 1(Fukae *et al.* 2009) (PDCD2-1) and striatal-enriched protein tyrosine phosphatase 61 (STEP61(Kurup *et al.* 2015)) were all found to accumulate in the SN or the striatum of PD brain. Of interest, increased levels of S-nitrosylated parkin(Sunico *et al.* 2013; Chung *et al.* 2004) were also observed in parkinsonian brain, a modification thought to decrease its E3 ubiquitin ligase activity(Chung *et al.* 2004). Moreover, increased phosphorylated parkin levels were also observed(Ko *et al.* 2006; Imam *et al.* 2011; Rubio de la Torre *et al.* 2009). This observation is of importance since phosphorylation inactivates parkin ubiquitin ligase function. According to several studies(Mahul-Mellier *et al.* 2014; Imam *et al.* 2011; Ko *et al.* 2006), this increased phosphorylation status would be the consequence of the increased level and activity of the non-receptor tyrosine kinase c-Abl. Finally, the parkin interactor nucleus accumbens 1 (NAC1) aggregated with parkin in dopaminergic neuron of the SN of PD patients(Korutla *et al.* 2014).

Other proteins associated with familial PD

Other proteins found associated with familial PD also presented abnormalities in the idiopathic form of the disease. PTEN-induced putative kinase 1(Muqit *et al.* 2006) (PINK1) and leucine-rich repeat kinase 2(Cho *et al.* 2013; Guerreiro *et al.* 2013) (LRRK2) levels are increased in the brain of PD patients, while ubiquitin C-terminal hydrolase-1 (UCHL-1) levels were found reduced in the SN(Barrachina *et al.* 2006). Interestingly, oxidized levels of DJ-1, which is considered as an oxidative stress sensor, are elevated in PD dopaminergic neurons(Choi *et al.* 2014). Of interest, levels and distribution of vacuolar protein sorting 35 homolog (VPS35), a component of retromer, remained unchanged in PD brain(Tsika *et al.* 2014).

Transition metals, calcium and calcium-binding proteins

Transition metals

Several studies indicate that metal homeostasis, particularly iron, is disrupted in PD (Table 3). Indeed, reports using different technologies indicated that iron levels are significantly increased in the SN of PD patients(Dexter *et al.* 1989; Ayton *et al.* 2013; Hirsch *et al.* 1991) and in the dopaminergic neurons populating this brain area(Oakley *et al.* 2007; Jellinger *et al.* 1992; Good *et al.* 1992), more precisely Fe^{3+} ion levels(Riederer *et al.* 1989). Increased iron has been linked to other pathogenetically relevant features of PD including oxidative stress and mitochondrial function(Mann *et al.* 1994). Moreover, several proteins that bind to or transport iron are also deregulated: the expression of such iron transport machinery like divalent metal transporter 1(Salazar *et al.* 2008) (DMT1), transferrin(Mastroberardino *et al.* 2009), Nedd4 family interacting protein 1(Howitt *et al.* 2014) (NDFIP1), a protein implicated in the posttranslational control of DMT1, the iron export protein ferroportin(Visanji *et al.*

2013), as well as the iron-binding proteins ferritin(Riederer *et al.* 1989), lactoferrin(Rousseau *et al.* 2013; Leveugle *et al.* 1996) and its receptor(Faucheux *et al.* 1995) are all increased in the SN of PD patients. Interestingly, ceruloplasmin, a protein acting as an iron-export ferroxidase, showed a decreased activity in the SN(Howitt *et al.* 2014).

Iron is not the only metal found dysregulated in PD. Total copper content is also decreased in the SN of PD patients(Dexter *et al.* 1989; Ayton *et al.* 2013), as well as the copper transporter 1 (CTR1). Interestingly, metallothioneins, proteins controlling the bioavailability of metals, including copper, were found to be overexpressed in the SN of PD patients. Aluminium and zinc content are increased in the SN of PD patients(Good *et al.* 1992; Hirsch *et al.* 1991), while manganese content is reduced in their putamen(Dexter *et al.* 1989).

Calcium and calcium-binding proteins

Calcium appears to be crucial for dopaminergic neuron survival since those of the SNpc expressing calbindin D-28K are less susceptible to degenerate in PD(Yamada *et al.* 1990). While total Ca^{2+} levels remain normal in PD (Table 3), voltage-gated Ca^{2+} channel (Ca_V) 1.2 and 1.3 levels are reduced in the SN of PD patients(Hurley *et al.* 2013) but not in their striatum(Watson *et al.* 1988). Parvalbumin levels, a protein expressed as a defensive response against Ca^{2+} stress, were also increased(Soós *et al.* 2004). There are conflicting reports on calcium binding proteins calbindin, calmodulin and calreticulin(Reynolds *et al.* 2008; Hurley *et al.* 2013; Wilhelmus *et al.* 2011b) while Ca^{2+}-dependent protein kinase (PKC) levels are decreased(Tanaka *et al.* 1993). The calcium dependent-protease calpain II is expressed by a larger number of neurons in the SN of PD patients(Mouatt-Prigent *et al.* 1996), contrary to its inhibitor calpastatin(Mouatt-Prigent *et al.* 2000). Finally, lipocortin-1, a Ca^{2+}-binding protein that buffers intracellular calcium involved in microglial activation, was reported to be

expressed by microglial cells, suggesting an ongoing inflammatory response(Knott *et al.* 2000).

Inflammation

While the central nervous system (CNS) is considered to be a relatively immune-privileged tissue, it is still able to initiate an immune response. This immune response is mediated by glial cells, usually initiated by microglial cells, the resident tissue macrophages of the CNS, and then amplified by astrocytes(Halliday and Stevens 2011). To maintain proper tissue homeostasis and to avoid collateral tissue damage during inflammatory reactions, all of the inflammatory responses must eventually be terminated. However, several studies indicate that an inflammatory response is ongoing in the parkinsonian brain (Table 4).

In PD brains, the number of microglial cells is increased(Lastres-Becker *et al.* 2012; Imamura *et al.* 2003) in comparison to control brains. Moreover, these cells are activated since the number of microglial cells expressing activation markers like HLA-DR(Orr *et al.* 2005; Imamura *et al.* 2003; Imamura *et al.* 2005), ICAM-1(Imamura *et al.* 2003), CD68(Vroon *et al.* 2007), lymphocyte function-associated antigen 1(Miklossy *et al.* 2006) (LFA-1), activated caspase-3/8(Burguillos *et al.* 2011), CD23(Hunot *et al.* 1999) or CD163(Pey *et al.* 2014) is also increased. Interestingly, microglial cells in PD brain express C1q(Depboylu *et al.* 2011), which is implicated in the clearance of apoptotic cells through phagocytosis. Additionally, increased levels of glucocorticoid receptors(Ros-Bernal *et al.* 2011), a regulator of inflammation, nitric oxide synthase(Hunot *et al.* 1996) (NOS) and inducible NOS(Knott *et al.* 2000) (iNOS), expression of which is increased during inflammatory events, as well as lipocortin-1(Knott *et al.* 2000), an anti-inflammatory molecule, were detected in microglial cells in PD brain.

In contrast to microglial cells, the activated status of astrocytes is more controversial in brains of PD patients, since some studies detect astrogliosis through increased expression of GFAP(Mythri *et al.* 2011; Lastres-Becker *et al.* 2012) or ICAM-1(Miklossy *et al.* 2006) while others did not(Mirza *et al.* 1999; Tong *et al.* 2015). However, whether astrogliosis is triggered or not, inflammatory events seemed to affect astrocytes since increased levels of myeloperoxidase(Choi *et al.* 2005a), a key oxidant-producing enzyme during inflammation, milk fat globule-EGF factor 8 (Kinugawa *et al.* 2013) (MFGE8), a factor involved in phagocytic recognition, as well as heme oxygenase-1(Schipper *et al.* 2009) (HO-1), an antioxidant enzyme involved in the regulation of the inflammatory process, were reported specifically in astrocytes in the parkinsonian brain. Importantly, infiltration of peripheral immune cells could also participates in the neuroinflammatory response in PD since LFA-1-positive leukocytes(Miklossy *et al.* 2006), CD8-positive and CD4-positive T cells(Brochard *et al.* 2009) were found in the SN of PD patients.

Inflammatory response can be harmful for the neuronal cells because of the release of pro-inflammatory agents. In the parkinsonian brain, higher levels of cytokines like interleukin (IL) 1β(Mogi *et al.* 1994a; Hunot *et al.* 1999) (IL-1β), IL-2(Mogi *et al.* 1996b), IL-6(Mogi *et al.* 1994a), tumor necrosis factor α(Mogi *et al.* 1994b; Hunot *et al.* 1999) (TNFα), S100B(Sathe *et al.* 2012), interferon ɣ(Mogi *et al.* 2007; Hunot *et al.* 1999) and its receptor(Hashioka *et al.* 2009), as well as chemokine (C-X-C motif) ligand 12 (CXCL12) and its receptor C-X-C chemokine receptor type 4(Shimoji *et al.* 2009) (CXCR4) were detected. Finally, at the neuronal level, inflammation appears ongoing since dopaminergic neurons of the SN express higher levels of cyclooxygenase-2(Teismann *et al.* 2003), the rate-limiting enzyme in prostaglandin E2 synthesis. Moreover, the nuclear fraction of NF-κB, a transcription factor activated during inflammatory response, is increased in the same neuronal population(Soós *et al.* 2004).

Mitochondrial abnormalities and oxidative stress

Mitochondrial abnormalities and energy deficits

Mitochondria play a prominent role in energy metabolism and many lines of evidence suggest mitochondrial dysfunctions and energy deficits in PD (Table 5). The first studies on mitochondrial dysfunction in PD documented deficiency of mitochondrial Complex I in the PD SN(Schapira *et al.* 1989; Schapira *et al.* 1990). Subsequent analyses have confirmed the important role of Complex I in PD(Morais *et al.* 2014). Other studies observed deregulated expression of several mitochondrial proteins in PD brain e.g. the molecular chaperones prohibitin(Ferrer *et al.* 2007), the outer mitochondrial membrane VDAC1(Chu *et al.* 2014), the mitochondrial import machinery translocase of outer membrane 40 TOM40(Bender *et al.* 2013), the serine protease HtrA2(Plun-Favreau *et al.* 2007), or hemoglobins α and β(Ferrer *et al.* 2011; Shephard *et al.* 2014). The PD associated protein parkin and PINK1 would also play a key role in mitochondrial dynamics (for review see (Pickrell and Youle 2015)). In this respect, AF6, a key regulator of PINK1/parkin-mediated autophagy, is less expressed in the SN of PD patients. Glucose metabolism is dysregulated in PD, particularly with the increased levels of pentose phosphate pathway enzymes glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) leading to elevated production of NADPH, a sign of oxidative stress(Dunn *et al.* 2014).

Finally, total and mitochondrial oxygen uptake(Navarro *et al.* 2009) is reduced. This is consistent with the evidences for impaired oxidative phosphorylation in PD brain samples(Keeney *et al.* 2006; Parker *et al.* 2008; Hattori *et al.* 1993; Navarro *et al.* 2009; Schapira *et al.* 1990; Schapira *et al.* 1989). Three reasons are evoked to explain this observation: complex I expression seemed to be reduced(Moisoi *et al.* 2009; Keeney *et al.* 2006), particularly the NADH dehydrogenase 6 subunit(She *et al.* 2011) (ND6); catalytic

subunits of complex I were found to contain oxidized proteins(Keeney *et al.* 2006); mitochondrial DNA may develop some mutations in PD (including the mitochondrial polymerase gamma gene(Orsucci *et al.* 2011)), which could explain defects in mitochondrial respiration(Sanders *et al.* 2014; Bender *et al.* 2006; Lin *et al.* 2013). ATP synthase levels have been reported to be reduced in the SN of PD patients(Ferrer *et al.* 2007). As a consequence of the deficit of mitochondrial electron transport chain, high-energy phosphates such as ATP and phosphocreatine as final acceptors of energy from mitochondrial oxidative phosphorylation are reduced. In contrast, low-energy metabolites such as ADP and inorganic phosphate were within normal ranges(Hattingen *et al.* 2009). Since complex I is considered as one of the main source of reactive oxygen species in the cell, its abnormal function could lead to increased oxidative stress. This could explain the observed increase in the oxidative damage of mitochondrial proteins(Navarro *et al.* 2009).

Oxidative stress

A large number of studies indicate that oxidative stress is considered as a major contributing factor in the pathogenesis of PD (Table 5). The levels of total oxidized proteins(Alam *et al.* 1997; Choi *et al.* 2005b; Yoritaka *et al.* 1996; Mythri *et al.* 2011) are highly increased in several brain areas, either through carbonylation or nitrosylation, and more particularly mitochondrial proteins(Shimura-Miura *et al.* 1999; Navarro *et al.* 2009). Moreover, oxidative stress sensor of nucleolar integrity is disrupted in dopaminergic neurons of the SN(Rieker *et al.* 2011), while Nrf2 (nuclear factor erythroid 2-related factor 2), which is translocated into the nucleus in response to oxidative stress, shows increased nuclear and reduced cytoplasmic levels(Ramsey *et al.* 2007). Antioxidant proteins levels and activities are particularly deregulated: biliverdin reductase(Reynolds *et al.* 2008), superoxide dismutase (SOD)(Radunović *et al.* 1997; Marttila *et al.* 1988; Choi *et al.* 2005b; Ferrer *et al.* 2007;

Navarro *et al.* 2009), sestrin-2(Zhou *et al.* 2013), selenoprotein P(Bellinger *et al.* 2012), osteopontin(Maetzler *et al.* 2007), NAD(P)H quinone oxidoreductase(van Muiswinkel *et al.* 2004), MTH1(Nakabeppu *et al.* 2007), MUTYH(Arai *et al.* 2006; Shimura-Miura *et al.* 1999) (mutY Homolog), nitrosylated peroxiredoxin-2(Fang *et al.* 2007), levels and/or activities are increased, while catalase and peroxidase activity(Ambani *et al.* 1975) are decreased. This decrease in peroxidase activity can be controlled through phosphorylation. Interestingly, phosphorylated peroxyredoxin-2 and 3 levels are increased in the PD brain(Qu *et al.* 2007; Angeles *et al.* 2011).

The glutathione system, which is responsible for the detoxification of reactive oxygen and nitrogen species, appeared to be deregulated in PD patients. While oxidized glutathione levels are normal, reduced glutathione levels are severely decreased in the SN of PD patients(Sian *et al.* 1994; Pearce *et al.* 1997; Riederer *et al.* 1989). Moreover, several enzymes of the glutathione system including ɣ-glutamyltranspeptidase(Mythri *et al.* 2011; Sian *et al.* 1994), glutathione peroxidase(Power *et al.* 2002; Mythri *et al.* 2011), glutathione-S-transferase(Reynolds *et al.* 2008) levels and/or activities are altered in the PD brain.

One consequence of oxidative stress in PD is DNA damage. Indeed, in PD patients, DNA is severely oxidized(Du *et al.* 2009), and mitochondrial and nuclear DNA presented a higher number of mutations(Zhang *et al.* 2002; Ozawa *et al.* 1997; Lin *et al.* 2013; Sanders *et al.* 2014; Bender *et al.* 2006) than control brains. In response to DNA damage, defense mechanisms against oxidative damage to nucleic acids involving MTH1(Shimura-Miura *et al.* 1999), MUTYH(Arai *et al.* 2006) and OGG1 (8-oxoguanine DNA-glycosylase 1) (Fukae *et al.* 2005) as well as DNA repair proteins such as poly(ADP-ribose) polymerase(Soós *et al.* 2004) (PARP), TNF Receptor Associated Protein(Vilotti *et al.* 2012) (TRAPP), DNA polymerase δ(Camins *et al.* 2010) and ataxia telangiectasia muted(Camins *et al.* 2010) (ATM) are activated in PD brain.

Abnormal protein removal and degradation

The ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP) are the two most important cellular mechanisms that repair or remove abnormal proteins(Korolchuk *et al.* 2010). Since PD is characterized by the presence of misfolded and aggregated proteins that forms Lewy bodies, alterations in abnormal protein removal could be implicated in its pathogenesis through impairment of either UPS, ALP, or both mechanisms (Table 6).

Ubiquitin-proteasome system (UPS)

The UPS is the principal mechanism for protein catabolism in the mammalian cytosol and nucleus. Degradation of a protein via the UPS involves two steps: the conjugation, which consists in the covalent attachment of ubiquitin molecules to the substrate protein, and the subsequent degradation of the tagged protein by the proteasome(Korolchuk *et al.* 2010). Several lines of evidence obtained from the postmortem study of PD brains suggest that the UPS is dysregulated in this pathology (Table 6). First, total ubiquinated protein level is dramatically increased in the striatum of PD patients(Lonskaya *et al.* 2013). This could be the result of defective expression of several ubiquitin ligase or deubiquitinase. In line with this hypothesis, SKP1A(Mandel *et al.* 2007) (S-phase kinase-associated protein 1A), NEDD4(Tofaris *et al.* 2011) (neural precursor cell expressed, developmentally down-regulated 4), USP9X(Rott *et al.* 2011) (ubiquitin specific peptidase 9, X-linked) and TRIM9(Tanji *et al.* 2010) (tripartite motif containing 9) have been shown to be deregulated in the SN of parkinsonian brains. Also, parkin, a protein encoded by a gene that when mutate, is associated with familial PD, possesses ubiquitin ligase activities(Seirafi *et al.* 2015).

The increase in total ubiquinated protein level could also be explained by proteasomal dysfunctions. Indeed, the activity of the 26S proteasome is decreased in several structures of the parkinsonian brain(Wills *et al.* 2010). The 20S proteasome, which correspond to the catalytic core of the protein complex, is also underexpressed(McNaught and Jenner 2001; Chu *et al.* 2009; Wills *et al.* 2010), explaining its weaker chymotriptic, tryptic and postacidic activities(McNaught *et al.* 2003; McNaught and Jenner 2001) in the SN of PD brains. More precisely, the α-subunit of 20S proteasome is underexpressed in this structure(McNaught *et al.* 2003), a result confirmed by Bukhatwa et al.(Bukhatwa *et al.* 2010) who reported that α4 and α6 subunit levels were specifically decreased in dopaminergic neurons of the SN. This decrease in α subunits of the 20S appears to be restricted to the SN since α6 subunit levels are increased in the striatum(Nakamura *et al.* 2006). Likewise, the regulatory core of the proteasome called 19S (or PA700) has also been reported to be underexpressed in the SN but overexpressed in the Str(McNaught *et al.* 2003). PA28 (also known as 11S), an alternate regulator that can replace 19S proteasome, did not seem to be involved in the pathology(McNaught *et al.* 2003).

Lysosome, macroautophagy and chaperone-mediated autophagy (CMA)

Autophagy is a cellular process by which cytoplasmic materials are delivered to and degraded in the lysosome to maintain cellular homeostasis. Depending on the mode of cargo delivery to the lysosome, autophagy can be subdivided into three subtypes: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA)(Wu *et al.* 2014). While microautophagy had not been assessed in parkinsonian brains, evidence suggests that macroautophagy, CMA and lysosomal degradation are deregulated in PD patients (Table 6).

Macroautophagy, which is the most universal form of autophagy, is characterized by the formation of autophagosomes that are capable of disposing of protein aggregates and

damaged organelles(Korolchuk *et al.* 2010). Macroautophagy appears to be implicated in PD pathogenesis since several key proteins driving this cellular process are deregulated. Beclin-1, which is responsible for the formation and the maturation of autophagosomes, is increased in the SN of PD patients(Rohn and Catlin 2011; Miki *et al.* 2015), as well as LC3II(Dehay *et al.* 2010), an autophagosome marker. However, no difference was observed between control and PD levels of unc-51 like autophagy activating kinase 1 (ULK1), ULK2 or phosphatidylinositol 3-kinase VPS34(Miki *et al.* 2015). In contrast to autophagy, CMA is a process by which selected cytosolic proteins are directly targeted to the lysosome for degradation (for more details see (Kaushik and Cuervo 2012)). Impairment of CMA function is implicated in PD pathogenesis since heat shock cognate 70(Alvarez-Erviti *et al.* 2010; Mandel *et al.* 2009) (HSC70), a protein responsible for the translocation of targeted substrate into the lysosome, as well as its lysosomal surface receptor lysosomal-associated membrane protein 2(Murphy *et al.* 2014; Alvarez-Erviti *et al.* 2010) (LAMP2) are less expressed in several structures of PD brain. This deficit in CMA in PD brain could explain why levels of MEF2D (myocyte enhancer factor 2D), a transcription factor degraded through CMA, are increased in the striatum of PD patients(She *et al.* 2011).

At the lysosomal level, Anglade and coworkers(Anglade *et al.* 1997) observed that the number of autophagic vacuoles is drastically decreased in the dopaminergic neurons of PD SN. At the molecular level, lysosomal markers like the structural protein Lysosome Associated Membrane Protein 1(Chu *et al.* 2009; Dehay *et al.* 2010) (LAMP1), the lysosomal P-type ATPase ATP13A2(Dehay *et al.* 2012), glucocerebrosidase(Gegg *et al.* 2012; Murphy *et al.* 2014) and its interacting partner lysosomal integral membrane protein type-2(Rothaug *et al.* 2014) (LIMP-2) as well as Heat Shock Protein 73(Chu *et al.* 2009) (HSP73), all were decreased in the SN of PD patients. Moreover, several enzymes that participate in the degradation of proteins (Cathepsins A(Murphy *et al.* 2014), B(Mantle *et al.* 1995), D(Murphy

et al. 2014; Chu *et al.* 2009; Mantle *et al.* 1995), H(Mantle *et al.* 1995), L(Mantle *et al.* 1995), and dipeptidyl aminopeptidase(Mantle *et al.* 1996)) had abnormal levels or activities. Interestingly, the expression of two transcription factors crucially involved in the ALP, namely transcription factor EB(Decressac *et al.* 2013) (TFEB) and LMX1B(Laguna *et al.* 2015) (LIM homeobox transcription factor 1 beta), were found to be reduced in the dopaminergic neurons of the SN of PD patients.

Apoptosis and transduction pathways

Several lines of evidence suggest that neurons degenerate mostly through an apoptotic pathway in PD. The SN of PD patients contains hallmarks of apoptosis, such as nuclear condensation, chromatin fragmentation(Tompkins *et al.* 1997) or TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) positive cells(Mochizuki *et al.* 1996). At the molecular level, two different routes can trigger caspase-mediated apoptotic processes: the intrinsic and the extrinsic apoptotic pathway (Table 7). Since the intrinsic apoptosis pathway is activated following intracellular events such as ER stress or cell cycle re-entry, we will first review these topics.

ER stress

ER is recognized as the site of synthesis and folding of proteins. Abnormalities in ER functions lead to the accumulation and aggregation of unfolded proteins. To avoid this protein accumulation, transmembrane receptors located in the ER detect the onset of ER stress and activate the unfolded protein response (UPR). If UPR fails in reinstating normal ER function, apoptotic cell death ensues (for review see (Szegezdi *et al.* 2006)). Few studies have focused on ER stress and UPR markers in PD brains (Table 7). Hoozemans et al. showed that an increased number of dopaminergic neurons of the SN express the UPR activation markers

phosphorylated pancreatic ER kinase (PERK) and phosphorylated eukaryotic initiation factor 2α (eIF2α)(Hoozemans *et al.* 2007), as well as phosphorylated inositol-requiring enzyme 1 (IRE1α)(Hoozemans *et al.* 2012). In another study, increased nuclear levels of activated, phosphorylated double-strand RNA dependent protein kinase (PKR), a kinase which activates eIF2α, were also reported(Bando *et al.* 2005). Finally, homocysteine-induced endoplasmic reticulum protein (HERP), a stress-response protein localized in the ER membrane, is also overexpressed in the SN of PD patients(Slodzinski *et al.* 2009).

Cell cycle re-entry

Recent results indicate that re-entry into the cell cycle may constitute a common pathway involved during neurodegeneration(Folch *et al.* 2012). Consistent with this hypothesis (Table 7), neurons with extra copies of chromosomes 18 and X(Höglinger *et al.* 2004) as well as increased levels of normal and phosphorylated retinoblastoma protein (pRb), a molecular trigger of cell-cycle progression, were observed in dopaminergic neurons in the postmortem SN of PD patients(Jordan-Sciutto *et al.* 2003). Moreover, p25/Cdk5 (cyclin-dependent kinase 5), which phosphorylates pRb(Hamdane *et al.* 2005), is overexpressed in PD(Alvira *et al.* 2008; Rubio de la Torre *et al.* 2009), as well as the Cdk5 activator p35(Rubio de la Torre *et al.* 2009). In line with this view, SN dopaminergic neurons of PD patients has been shown to be immunoreactive for proliferating cell nuclear antigen(Höglinger *et al.* 2004) (PCNA), a subunit of DNA polymerase, E2F-1, a mitosis-linked transcription factor(Höglinger *et al.* 2004; Alvira *et al.* 2008), and cyclin D1(Camins *et al.* 2010).

Intrinsic apoptotic pathway

Cellular stress such as ER stress or DNA damage activates B cell lymphoma 2 (BCL-2) homology 3 (BH3)-only proteins leading to BCL-2-associated X protein (Bax) activation.

Interestingly, Bax levels were shown to be increased specifically in dopaminergic neurons(Tatton 2000), and in Lewy body containing neurons(Hartmann *et al.* 2001a). The anti-apoptotic Bcl-2, which binds activated Bax, was shown to be overexpressed in several structures of PD brains(Letters *et al.* 1996; Marshall *et al.* 1997). Once activated, Bax triggers mitochondrial outer membrane permeabilisation. As a consequence, cytochrome c is released into the cytosol. In PD SN and LC, neurons exhibit a higher level of cytochrome c(Kawamoto *et al.* 2014). Moreover, total cytochrome c content is increased in PD temporal cortex while mitochondrial content is decreased(Jiang *et al.* 2012). Consistent with a permeabilisation of the mitochondrial membrane, endonuclease G, a mitochondrial pro-apoptotic nuclease, is also found in the nucleus of PD dopaminergic neurons(Büttner *et al.* 2013). Once released in the cytosol, cytochrome c binds apoptotic protease-activating factor 1 (APAF1), inducing its oligomerization and thereby forming a structure termed the apoptosome that recruits and activates an initiator caspase, caspase 9. In TH neurons of PD SN, increased levels of both APAF1(Kawamoto *et al.* 2014) and activated caspase-9(Viswanath *et al.* 2001; Kawamoto *et al.* 2014) have been reported. When activated, caspase-9 cleaves and recruits executioner caspase-3, leading to apoptosis. In PD brain, caspase-3 activity(Mogi *et al.* 2000) and levels(Tatton 2000; Jiang *et al.* 2012) are increased in the SN and temporal cortex. In contrast to these observations, Hartmann et al.(Hartmann *et al.* 2000) observed a significant decrease of caspase-3-positive pigmented neurons in the SNpc of PD patients compared to controls, interpreted as an increased sensitivity to the pathological process of caspase-3 containing neurons. Finally, p53 and its active, phosphorylated form (pp53), a transcription factor that controls the expression and the activation of several proteins implicated in the apoptotic process (including Bax and Apaf1), is overexpressed in several brain areas of PD patients(Mogi *et al.* 2007; Sunico *et al.* 2013; Camins *et al.* 2010).

Extrinsic pathway

The activation of the extrinsic apoptotic pathway depends on external factors(Elmore 2007) that as previously mentioned, could be involved in PD pathogenesis, such as neurotrophic factor deprivation or inflammation. During inflammatory episodes, cytokines and pro-inflammatory agents like TNF-α or FasL are released by glial cells. These pro-inflammatory agents can trigger the extrinsic apoptotic pathway by interacting with TNF receptor (TNFR) family. Interestingly, in PD postmortem brains, TNF receptor I (TNFRI, also known as p55) and its effector protein TNFR1-associating protein with a death domain (TRADD) levels have both been shown to be increased in the SN(Mogi *et al.* 2000) and the temporal cortex(Jiang *et al.* 2012). Reduced expression of Fas, another receptor potentially responsible for the activation of the extrinsic apoptotic pathway, and its ligand FasL have been observed in neurons of the SN of PD patients, while their levels were increased in reactive astrocytes of the same structure(Ferrer *et al.* 2000). Mogi(Mogi *et al.* 1996a) et al., showed that soluble Fas expression was increased in the caudate nucleus and putamen of parkinsonian brains. Moreover, levels of Fas-associated factor-1, which can serve as an enhancer of apoptosis initiated through Fas, was overexpressed(Betarbet *et al.* 2008).

Activation of TNFRI or Fas by pro-inflammatory agents converges with the activation by cleavage of caspase-8. Increased levels of activated caspase-8 have been observed in dopaminergic neurons of the SN in PD patients(Viswanath *et al.* 2001), and an increased number of TH neurons of the same structure expressing activated caspase-8 was also reported(Hartmann *et al.* 2001b). Of interest, the number of TH neurons expressing Fas-associating protein with a death domain (FADD), which participates in the auto-proteolytic cleavage of caspase-8, is reduced in the SN of PD patients, suggesting that these neurons are more prone to degeneration(Hartmann *et al.* 2002). Once activated, caspase-8 may in turn cleave effector caspases such as caspase-3 or caspase-1, whose activities are increased in the

SN of PD patients(Mogi *et al.* 2000). Moreover, Bid and its post-translationally activated, truncated form tBid through caspase-8-mediated cleavage, are also increased in the cytoplasm and mitochondria of PD brains(Jiang *et al.* 2012).

Other form of cell death

Lee and coworkers(Lee *et al.* 2013) demonstrated that parthanatos, a form of cell death induced by excessive poly-ADP-ribose polymers, could be implicated in PD since the level of these polymers is strongly increased as well as AIMP2, which is thought to mediate parthanatos-induced cell death.

Transduction pathways and transcription factors

Several changes in the activation of transcription factors and transduction pathways occur in PD brain (Table 7). Since cellular stress might be of great importance in PD pathogenesis, many studies focused on nuclear factor-kappa B (NF-κB), a transcription factors involved in cellular responses to inflammation and oxidative stress(Morgan and Liu 2011). Many lines of evidence suggest that NF-κB is activated in PD. First, negative regulator of NF-κB activation like RING finger protein 11 (RNF11) has reduced expression in PD(Pranski *et al.* 2013). Total NF-κB levels were found elevated in the SN of PD patients(Mogi *et al.* 2007), as well as its constituting subunit p50(Reynolds *et al.* 2008) and p65(Ghosh *et al.* 2009; Reynolds *et al.* 2008). These increased levels were found in the cytosol as well as in the nucleus(Reynolds *et al.* 2008). Interestingly, increased nuclear levels are reported in the dopaminergic neurons of the SN of PD patients(Hunot *et al.* 1997; Soós *et al.* 2004). Moreover, levels of normal and phosphorylated p53 protein, known to be involved in apoptosis, are increased in PD brains(Mogi *et al.* 2007; Folch *et al.* 2012; Sunico *et al.* 2013).

Akt, a prosurvival factor(Zhang *et al.* 2011), appears to be involved in the pathogenesis of PD since its midbrain levels are significantly reduced(Timmons *et al.* 2009). This was also observed in TH neurons of the SN(Malagelada *et al.* 2008), and phosphorylated levels of GSK-3β (Glycogen synthase kinase-3β), which is negatively regulated by Akt, are increased in PD striatum(Wills *et al.* 2010). Importantly, levels of S473-phosphorylated (activated) Akt were reduced in this neuronal population(Malagelada *et al.* 2008) in TH neurons. To explain this observation, Malagelada et al. suggested the involvement of Redd1, an endogenous inhibitor of Akt expression and activation, which levels are increased in the parkinsonian SN(Malagelada *et al.* 2008).

The microtubule-associated protein kinase (MAPK) pathway is important for cell survival(Cargnello and Roux 2011). One of its members, $ERK_{1/2}$ (Extracellular signal-regulated kinase 1/2), and its downstream target CREB (cAMP response element-binding) were reported as less phosphorylated in PD striatum(Kurup *et al.* 2015). Contrasting results were observed in the frontal cortex of PD patients(Price *et al.* 2010). Two other members of the MAPK family, the prodeath c-Jun N-terminal kinase (JNK) and p38, displayed increased levels in the SN of PD patients(Hu *et al.* 2011). Accordingly, Hunot et al. reported increased activated JNK downstream target c-jun in PD dopaminergic neurons(Hunot *et al.* 2004). Of interest, apoptosis signal-regulating kinase 1 (ASK1), which regulated the activation of both JNK and p38, was also found to be more activated(Hu *et al.* 2011). Moreover, membrane levels of 14-3-3ζ phosphorylated at S58, which causes release of the pro-apoptotic protein ASK1 and cell death in response to oxidative stress(Zhou *et al.* 2009), are decreased in PD patients(Slone *et al.* 2015). Finally, a number of other transcription factors crucially involved in cell survival following cellular stress such as PGC1α(Eschbach *et al.* 2015; Shin *et al.* 2011) (peroxisome proliferator-activated receptor gamma, coactivator 1 alpha), MEF2D(Gao *et al.* 2014; Chu *et al.* 2011; She *et al.* 2011) or Nurr1(Chu *et al.* 2006) (Nuclear receptor

related 1) are underexpressed in PD brain, while Nfatc4 (Nuclear Factor Of Activated T-Cells, Cytoplasmic, Calcineurin-Dependent 4) nuclear localization is increased(Caraveo *et al.* 2014).

Other proteins

Expression of several other proteins have also been shown to be altered in PD and in particular structural and cytoskeleton proteins. Connexin-36(Schwab *et al.* 2014) and α-tubulin(Reynolds *et al.* 2008) levels are increased, while actin(Reynolds *et al.* 2008) and L-plastin(Reynolds *et al.* 2008) are reduced. Abnormal microtubule-associated protein 2 (MAP-2) nuclear labelling has been reported(D'Andrea *et al.* 2001). Of interest, tau phosphorylation status is, as in Alzheimer's disease, highly modified(Duka *et al.* 2013; Wills *et al.* 2010). Levels of synaptic proteins like the SNARE assembly complex(Sharma *et al.* 2012), SNAP-25 or syntaxin-1(Garcia-Reitböck *et al.* 2010)are all modified as well as extracellular matrix components MMP-2 (matrix metalloprotease 2) and TIMP-1(Lorenzl *et al.* 2002) (TIMP Metallopeptidase Inhibitor 1), lipid transporters apolipoprotein (apo) D(Ordoñez *et al.* 2006) (ApoD), E(Wilhelmus *et al.* 2011a) (ApoE) and ApoE receptor LRP1(Wilhelmus *et al.* 2011a). Finally, the expression of several phospholipid biosynthetic enzymes as calcium-stimulated phospholipase A2, phosphatidylserine synthase, phosphocholinecytidylyltransferase and phosphoethanolaminecytidylyltransferase are also increased(Ross *et al.* 2001).

Incidental Lewy body disease

Incidental Lewy body disease (ILBD) is usually considered as a prodromal state of PD characterised by the absence of motor symptoms but the presence of a variety of non-motor abnormalities. At the cellular level, ILBD is characterised by a moderate nigral neuronal loss(Dijkstra *et al.* 2014) and Lewy pathology(Iacono *et al.* 2015), decreased striatal

dopaminergic immunoreactivity(DelleDonne *et al.* 2008; Dickson *et al.* 2008; Beach *et al.* 2008), olfactory bulb abnormalities(Driver-Dunckley *et al.* 2014), and microglial activation(Doorn *et al.* 2014). However, few studies have focused on the molecular changes. L-ferritin and copper levels are decreased(Davies *et al.* 2014),(Koziorowski *et al.* 2007), while mitochondrial DNA mutations(Lin *et al.* 2012) and Bcl-2(Marshall *et al.* 1997) levels are increased. Several evidences suggest that oxidative stress and mitochondrial function are also altered in ILBD(Dexter *et al.* 1994; Dalfó *et al.* 2005).

Conclusions

There are comprehensive data derived from postmortem PD brains that have demonstrated that multiple pathways and cellular functions are modified at the molecular level in late-stage pathology. During our review of the literature, we observed that postmortem studies were mainly restricted to the nigrostriatal pathway, while cerebral structures that are affected before this pathway during the course of the disease (i.e. olfactory bulb and medulla oblongata(Goedert *et al.* 2014)) or where cell loss is also important in the disease (such as locus coeruleus(Zarow *et al.* 2015) and pedunculopontine nucleus(Hirsch *et al.* 1987)) are poorly studied at the molecular level. This is a disadvantage in our efforts to understand the effects of pathogenesis on non-dopaminergic systems and in particular the biochemical changes that underlie non-motor features in PD. In addition, there is an opportunity by this means to investigate areas 'ahead of the pathology' i.e. those regions that might be affected by early molecular derangements, but not neurodegeneration. This would provide insight into the evolving nature of the molecular pathogenesis of PD, and represent the same principle as addressed in those studies on Incidental Lewy Body disease (see above) but in pathologically proven PD brain. Animal studies in PD field focus exclusively on nigrostriatal cell

degeneration and death, which could somehow explain the high rate failure of drugs that were tested successfully in animal models but failed clinically in PD patients.

On the other hand, while postmortem brain studies represent an efficient way to improve our understanding of the pathology, it also presents some limitations. The sample size is often limited because it is still difficult to obtain brain tissue, and postmortem delay will affect the quality of tissues, and thus the preservation of proteins especially when some are more vulnerable than others(Ferrer *et al.* 2008). Braak stage of collected postmortem brains is also usually highly heterogeneous, challenging further comparisons. These factors, together with heterogeneity of PD could render the interpretation of postmortem studies very difficult, even sometimes uncertain if sampling is not rigorously performed.

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Conflicts of interest

The authors declare no conflicts of interest.

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Table 1. Neurotransmitters and neurotrophic factors changes observed in the human parkinsonian brain at the protein level. Legend: Am: Amygdala; Ca: Caudate nucleus; Cb: Cerebellum; Cb Cx: Cerebral cortex; Cg Cx: Cingulate cortex; Cg Gy: Cingulate gyrus; Fr Cx: Frontal cortex; Fr Gy: Frontal gyrus; GP: Globus pallidus; Hp: Hippocampus; LC: Locus coeruleus; NAcc: Nucleus accumbens; nb: number; NBM: Nucleus basalis of Meynard; Oc Cx: Occipital cortex; PPN: pedunculopontine nucleus; Pu: Putamen; SN: Substantia nigra; STN: Subthalmic nucleus; Str: Striatum; Th: Thalamus; Tp Cx: Temporal cortex.

Table 2. PD-linked genes changes observed in the human parkinsonian brain at the protein level. Legend: see Table 1.

Table 3. Calcium and transition metal-related proteins changes observed in the human parkinsonian brain. Legend: see Table 1.

Table 4. Changes neuroinflammatory-related proteins observed in the human parkinsonian brain. Legend: see Table 1.

Table 5. Changes in mitochondrial and oxidative stress-related proteins observed in the human parkinsonian brain. Legend: see Table 1.

Table 6. Changes in ubiquitin proteasome system, lysosomal and autophagy proteins observed in the human parkinsonian brain. Legend: see Table 1.

Table 7. Changes in apoptosis-related proteins observed in the human parkinsonian brain. Legend: see Table 1.

Table 8. Changes in transcription factors and transduction pathways observed in the human parkinsonian brain. Legend: see Table 1.

Table 1. Neurotransmitters and neurotrophic factors observed in the human parkinsonian brain at the protein level. Legend: Am: Amygadala; Ca: Caudate nucleus; Cb: Cerebellum; Cb Cx: Cerebral cortex; Cg Cx: Cingulate cortex; Cg Gy: Cingulate gyrus; Fr Cx: Frontal cortex; Fr Gy: Frontal gyrus; GP: Globus pallidus; Hp: Hippocampus; LC: Locus coeruleus; NAcc: Nucleus accumbens; nb: number; NBM: Nucleus basalis of Meynard; Oc Cx: Occipital cortex; PPN: pedunculopontine nucleus; Pu: Putamen; SN: Substantia nigra; STN: Subthalmic nucleus; Str: Striatum; Th: Thalamus; Tp Cx: Temporal cortex.

Protein	**Ref**	**Structure**	**Observation in PD**
Neurotransmitters, transporters and receptors			
5-S-Cysteinyl-DOPA	(Spencer *et al.* 1998)	SN	↑ levels
5-S-Cysteinyl-DOPA	(Spencer *et al.* 1998)	GP, Ca, Pu	= levels
5-S-Cysteinyl-DOPAC	(Spencer *et al.* 1998)	SN	↑ levels
5-S-Cysteinyl-DOPAC	(Spencer *et al.* 1998)	GP, Ca, Pu	= levels
5-S-Cysteinyl-Dopamine	(Spencer *et al.* 1998)	SN	↑ levels
5-S-Cysteinyl-Dopamine	(Spencer *et al.* 1998)	GP, Ca, Pu	= levels
A2A receptor	(Varani *et al.* 2010)	Pu	↑ level and density
A2A receptor	(Villar-Menéndez *et al.* 2014)	Str	↑ levels in medium spiny neurons
AchE	(Xuereb *et al.* 1990)	Th	= activity
AchE	(Xuereb *et al.* 1990)	STN	↓ activity
AchR	(Griffiths *et al.* 1990)	Ca, Pu, Tp Cx	= density
AchR	(Griffiths *et al.* 1990)	GP	↑ density
AchR	(Gotti *et al.* 2006)	Str	↓ density
AchR (nicotinic)	(Court *et al.* 2000)	Ca, Pu	↓ density
AchR (nicotinic)	(Xuereb *et al.* 1990)	STN,Th, Tp Cx	= density
AchR (α2 subunit)	(Gotti *et al.* 2006)	Str, Tp Cx	= levels
AchR (α3 subunit)	(Gotti *et al.* 2006)	Str, Tp Cx	= levels
AchR (α4 subunit)	(Gotti *et al.* 2006)	Tp Cx	= levels
AchR (α4 subunit)	(Gotti *et al.* 2006)	Cb Cx, Str	↓ levels
AchR (α5 subunit)	(Gotti *et al.* 2006)	Str, Tp Cx	= levels
AchR (α6 subunit)	(Gotti *et al.* 2006)	Tp Cx	= levels
AchR (α6 subunit)	(Gotti *et al.* 2006)	Str	↓ levels
AchR (α7-subunit)	(Burghaus *et al.* 2003)	Cb Cx	↓ levels
AchR (α7-subunit)	(Banerjee *et al.* 2000)	Tp Cx	↓ nb of neurons
AchR (β2 subunit)	(Gotti *et al.* 2006)	Tp Cx	= levels
AchR (β2 subunit)	(Gotti *et al.* 2006)	Str	↓ levels

AchR (β3 subunit)	(Gotti *et al.* 2006)	Tp Cx	= levels
AchR (β3 subunit)	(Gotti *et al.* 2006)	Str	↓ levels
AchR (β4 subunit)	(Gotti *et al.* 2006)	Str, Tp Cx	= levels
Angiotensin II receptor	(Allen *et al.* 1992)	Ca, Pu, SN	↓ levels
Arginine vasopressin	(Leake *et al.* 1991)	Oc Cx, Tp Cx	= levels
Asparagine	(Gerlach *et al.* 1996)	Ca, Fr Cx, GP, Nacc, Pu, SN, STN, Th	= levels
Aspartate	(Gerlach *et al.* 1996)	Ca, Fr Cx, GP, Nacc, Pu, SN, STN, Th	= levels
Beta-arrestin	(Price *et al.* 2010)	Ca, Fr Cx, Hp	↑ cytosolic levels
ChAT	(Rinne *et al.* 1989),(Mattila *et al.* 2001), (Gotti *et al.* 2006)	Fr Cx, Hp, NBM, pFr Cx, Tp Cx	↓ activity
ChAT	(Xuereb *et al.* 1990), (Gotti *et al.* 2006)	STN, Str, Th	= activity
CRH	(Leake *et al.* 1991)	Oc Cx, Tp Cx	= levels
D1R	(Mattila *et al.* 2001),(Piggott *et al.* 1999),(Griffiths *et al.* 1994),	Ca, Nacc, Pu	= levels and density
D2R	(Griffiths *et al.* 1994), (Varani *et al.* 2010)	Ca, Pu	= density
D2R	(Piggott *et al.* 2007)	Th	↑ levels
D2R	(Mattila *et al.* 2001)	Ca, Pu	= levels
D2R	(Piggott *et al.* 1999)	Ca, Nacc, Pu	↑ density
D2R	(Ahlskog *et al.* 1991)	Pu	↓ density
D3R	(Piggott *et al.* 1999)	Ca, Nacc, Pu	= density
DAT	(Ryoo *et al.* 1998), (Güzey *et al.* 2012)	Ca, Pu	↓ levels
DOPAC	(Gerlach *et al.* 1996)	GP, STN, SN, Fr Cx, Th	= levels
DOPAC	(Gerlach *et al.* 1996)	Ca, Fr Cx, Nacc, Pu	↓ levels
Dopamine	(Gerlach *et al.* 1996)	STN, Th, SN,	= levels
Dopamine	(Gerlach *et al.* 1996)	Ca, GP, Nacc, Pu	↓ levels
EAAC1	(Duerson *et al.* 2009)	SN	= levels
GABA	(Gerlach *et al.* 1996)	Str, Th	↓ levels
GABA	(Gerlach *et al.* 1996)	Ca, GP, Nacc, Pu, SN, STN	= levels
GABA receptor	(Lloyd *et al.* 1977)	SN	↓ density
GABA receptor	(Lloyd *et al.* 1977)	GP, Th	= density
$GABA_AR$	(Griffiths *et al.* 1994)	Ca, GP, Pu	↓ density
Glutamate	(Gerlach *et al.* 1996)	Ca, Fr Cx, GP, Nacc, Pu, SN, STN, Th	= levels
Glutamine	(Gerlach *et al.* 1996)	Ca, GP, Th	↑ levels
Glutamine	(Gerlach *et al.* 1996)	Fr Cx, Nacc, Pu, SN, STN	= levels
Glycine receptor	(de Montis *et al.* 1982)	SN	↓ density
Histamine-2 receptor	(Martinez-Mir *et al.* 1993)	Str	= levels
Histamine-3 receptor	(Goodchild *et al.* 1999)	Ca, Cx, GP, Nacc, Pu, SN	= levels
HVA	(Gerlach *et al.* 1996)	Ca, Nacc, Pu	↓ levels
HVA	(Gerlach *et al.* 1996)	Fr Cx, GP, SN, STN, Th	= levels
MAO	(Gargalidis-Moudanos *et al.* 1997)	Pu	= activity
MAOB	(Gargalidis-Moudanos *et al.* 1997)	Cb Cx	= activity

mGluR5	(Price *et al.* 2010)	Ca, Fr Cx	↑ levels
mGluR5	(Price *et al.* 2010)	Hp	= levels
Muscarinic receptor	(Ahlskog *et al.* 1991)	Pu	↓ density
Muscarinic receptor	(Griffiths *et al.* 1994)	Pu	↑ density
Muscarinic receptor	(Griffiths *et al.* 1994)	Ca	= density
Muscarinic receptor M1	(Rinne *et al.* 1989)	Fr Cx, Hp, Tp Cx	= levels
Muscarinic receptor M2	(Rinne *et al.* 1989)	Fr Cx, Tp Cx	↑ levels
Muscarinic receptor M2	(Rinne *et al.* 1989)	Hp	= levels
Neuromelanin	(Halliday *et al.* 2006)	SN	↑ levels in TH neurons
Neurotensin receptor	(Uhl *et al.* 1986)	Mb	↓ density
NMDA Receptor	(Gerlach *et al.* 1996)	Ca	↓ density
NMDA Receptor	(Gerlach *et al.* 1996)	Fr Cx, GP, Nacc, Pu, SN, STN, Th	= density
NQO1	(van Muiswinkel *et al.* 2004)	SN	↑ levels in neurons and astrocytes
Opiate receptor (μ)	(Uhl *et al.* 1986)	Mb	↓ density
Opiate receptor (κ)	(Uhl *et al.* 1986)	Mb	↓ density
Serotonin transporter	(Güzey *et al.* 2012)	Ca, Cg Gy	↓ density
Serotonin-1 receptor	(Press and Waeber 1989)	Cx, Nacc, SN	= density
Somatostatin	(Leake *et al.* 1991)	Oc Cx, Tp Cx	= levels
Somatostatin receptor	(Uhl *et al.* 1986)	Mb	↓ density
TH	(Kastner *et al.* 1993)	SN	↓ level per neuron
TH	(Ryoo *et al.* 1998)	Pu	↓ levels
TH	(Ryoo *et al.* 1998)	Ca, GP	= levels
VMAT2	(Thibaut *et al.* 1995)	LC, Ra, SN	↓ density
VMAT2	(Miller *et al.* 1999)	Ca, Nacc, Pu	↓ levels
Neurotrophic factors			
BDNF	(Chauhan *et al.* 2001),(Mogi *et al.* 1999)	Str, SN	↓ levels
BDNF	(Mogi *et al.* 1999)	Cb, Fr Cx	= levels
BDNF	(Imamura *et al.* 2005)	Hp	↓ levels
BDNF	(Parain *et al.* 1999)	SN	↓ nb of expressing TH neurons
BDNF	(Knott *et al.* 2002)	SN	= levels in TH neurons
BDNF	(Knott *et al.* 2002)	SN	↑ nb of expressing astrocytes
bFGF	(Tooyama *et al.* 1994)	SN	↓ nb of expressing TH neurons
bFGF	(Mogi *et al.* 1996b)	Ca, Cx, Pu	= levels
CNTF	(Chauhan *et al.* 2001)	SN	↓ levels
CRH	(Hoogendijk *et al.* 1998)	PVN	= nb of expressing neurons
EGF	(Mogi *et al.* 1999)	Ca	↑ levels
EGF	(Mogi *et al.* 1999)	Cb Cx, Pu	= levels
EGF	(Iwakura *et al.* 2005)	pFr Cx, Str	↓ levels
ErbB1	(Iwakura *et al.* 2005)	pFr Cx, Str	↓ levels

ErbB2	(Iwakura *et al.* 2005)	pFr Cx, Str	↓ levels
ErbB3	(Iwakura *et al.* 2005)	pFr Cx, Str	= levels
ErbB4	(Iwakura *et al.* 2005)	pFr Cx, Str	= levels
ErbB4	(Depboylu *et al.* 2012)	SN	↑ proportion of expressing TH neurons
FGFR1	(Walker *et al.* 1998b)	SN	= levels in TH neurons
GDNF	(Mogi *et al.* 2001),(Chauhan *et al.* 2001)	Pu, SN	↓ levels
GDNF	(Mogi *et al.* 2001)	Ca	↑ levels
GDNF	(Mogi *et al.* 2001)	Cb, Fr Cx	= levels
HB-EGF	(Iwakura *et al.* 2005)	pFr Cx, Str	= levels
Insulin receptor	(Moroo *et al.* 1994)	PPN, SN	↓ levels
NGF	(Mogi *et al.* 1999)	SN	↓ levels
NGF	(Chauhan *et al.* 2001)	SN	= levels
NT-3	(Chauhan *et al.* 2001),(Knott *et al.* 2002)	SN, Str	= levels
NT-4	(Chauhan *et al.* 2001)	SN	= levels
Ret	(Decressac *et al.* 2012)	SN	↓ levels in TH neurons
Ret	(Walker *et al.* 1998a)	SN	= levels
TGFα	(Mogi *et al.* 1995)	Ca, Pu	↑ levels
TGFα	(Iwakura *et al.* 2005),(Mogi *et al.* 1995)	Cb Cx, pFr Cx, Str	= levels
TGF-β1	(Mogi *et al.* 1995)	Ca, Pu	↑ levels
TGF-β1	(Mogi *et al.* 1995)	Cb Cx	= levels
TrkB	(Knott *et al.* 2002)	SN, Str	= levels
TrkC	(Knott *et al.* 2002)	SN, Str	= levels

Table 2. PD-linked genes changes observed in the human parkinsonian brain at the protein level.
Legend: see Table 1.

Protein	Ref	Structure	Observation in PD
AF6	(Haskin *et al.* 2013)	Str, SN	↓ levels
AIMP2	(Imam *et al.* 2011),(Ko *et al.* 2010)	SN, Str	↑ levels
c-Abl	(Mahul-Mellier *et al.* 2014)	Cg Cx	↑ levels
c-Abl (phosphorylated at Y245)	(Imam *et al.* 2011),(Ko *et al.* 2010)	Str	↑ levels
c-Abl (phosphorylated at Y245)	(Imam *et al.* 2011),(Ko *et al.* 2010)	Cx, SN	= levels
DJ-1	(Bandopadhyay *et al.* 2004)	Fr Cx	= levels
DJ-1 (oxidized)	(Saito *et al.* 2014)	Str, SN	↑ levels
DJ-1 (S-nitrosylated)/ DJ-1 (total)	(Choi *et al.* 2014)	Fr Cx	↓ ratio
Dnmt1 (cytoplasm)	(Desplats *et al.* 2011)	Cx	↑ levels
Dnmt1 (nuclear)	(Desplats *et al.* 2011)	Cx	↓ levels
FBP1	(Imam *et al.* 2011),(Ko *et al.* 2010)	SN, Str	↑ levels
GRK5	(Arawaka *et al.* 2006)	SN	= levels
Jtv-1	(Kurup *et al.* 2015)	Str	↑ levels
LRRK2	(Guerreiro *et al.* 2013)	Ag, Cg Cx, Fr Cx	↑ levels
MMP3	(Choi *et al.* 2011)	SN	↑ levels
NAC1	(Korutla *et al.* 2014)	SN	aggregates with parkin in TH neurons
Parkin (aggregated)	(LaVoie *et al.* 2005)	Ca, Pu	↑ levels
Parkin (phosphorylated at S101)	(Rubio de la Torre *et al.* 2009)	Ca	↑ levels
Parkin (phosphorylated at S101)	(Rubio de la Torre *et al.* 2009)	Cb, Cx	= levels
Parkin (S-nitrosylated)	(Chung *et al.* 2004)	Cg Cx, SN, Tp Cx	↑ levels
Parkin (soluble)	(Lonskaya *et al.* 2013)	Str	↓ level
Parkin (total)	(Wills *et al.* 2010),(Rubio de la Torre *et al.* 2009),(LaVoie *et al.* 2005)	Ca, Cb, Cx, Fr Gy, Str	= levels
Parkin (tyrosine-phosphorylated)	(Imam *et al.* 2011),(Ko *et al.* 2010)	SN, Str	↑ levels
PARIS	(Shin *et al.* 2011)	SN, Str	↑ levels
PDCD2-1	(Fukae *et al.* 2009)	Mb	↑ levels
PINK1	(Muqit *et al.* 2006)	Cb, SN	↑ levels
PINK1	(Muqit *et al.* 2006)	Cx	= levels
SEPT4	(Shehadeh *et al.* 2009)	Ag, SN	↑ levels
SMG1	(Henderson-Smith *et al.* 2013)	Cg Cx	↓ levels
STEP61	(Kurup *et al.* 2015)	Str	↑ levels
Tissue transglutaminase	(Wilhelmus *et al.* 2011b),(Citron *et al.* 2002),(Andringa *et al.* 2004)	SN	↑ levels and activity, levels in TH neurons, nb of expressing TH neurons
UCHL-1	(Barrachina *et al.* 2006)	SN	↓ levels

UCHL-1	(Barrachina *et al.* 2006)	Fr Cx	= levels
USP9X	(Rott *et al.* 2011)	SN	↓ levels
VPS35	(Tsika *et al.* 2014)	Ca, Pu, Fr Cx	= levels
α-synuclein (calpain-cleaved)	(Dufty *et al.* 2007)	SN	↑ levels
α-synuclein (dimer/monomer)	(Sharon *et al.* 2003)	SN	↑ ratio
α-synuclein (insoluble)	(Wills *et al.* 2010)	Fr Gy, Str	↑ levels
α-synuclein (mitochondria)	(Devi *et al.* 2008)	SN, Str	↑ levels
α-synuclein (modified with acrolein)	(Shamoto-Nagai *et al.* 2007)	SN	↑ levels
α-synuclein (nitrated)	(Giasson *et al.* 2000)	Cg Cx, Am	↑ levels
α-synuclein (phosphorylated at S129)	(Mahul-Mellier *et al.* 2014)	Cg Cx	↑ levels
α-synuclein (phosphorylated at Y125)	(Mahul-Mellier *et al.* 2014)	Cg Cx	= levels
α-synuclein (phosphorylated at Y39)	(Mahul-Mellier *et al.* 2014)	Cg Cx	= levels
α-synuclein (soluble)	(Wills *et al.* 2010)	Fr Gy, Str	↑ levels
α-synuclein (total)	(Westerlund *et al.* 2008)	Cb	↓ levels

Table 3. Calcium and transition metal-related proteins changes observed in the human parkinsonian brain. Legend: see Table 1.

Protein or metal	Ref	Structure	Observation in PD
Transition metals			
Al (Total)	(Good *et al.* 1992)	SN	↑ levels in TH neurons
Al (Total)	(Hirsch *et al.* 1991)	SN	↑ levels
Ceruloplasmin	(Loeffler *et al.* 2006)	Hp	↑ levels
Ceruloplasmin	(Loeffler *et al.* 2006)	Fr Cx	↓ levels
Ceruloplasmin	(Ayton *et al.* 2013)	SN	↓ ferroxidase activity
Ceruloplasmin	(Ayton *et al.* 2013), (Loeffler *et al.* 2006)	Ca, Cb, Fr Cx, Pu, SN	= levels
Ceruloplasmin	(Ayton *et al.* 2013)	Fr Cx	= activity
CTR1	(Davies *et al.* 2014)	SN	↓ levels
Cu (Total)	(Riederer *et al.* 1989)	Rp	↑ levels
Cu (Total)	(Dexter *et al.* 1989),(Ayton *et al.* 2013)	SN	↓ levels
Cu (Total)	(Dexter *et al.* 1989),(Ayton *et al.* 2013),(Riederer *et al.* 1989)	Ca, Cb, Cx, Fr Cx, GP, Pu, SN	= levels
DMT1	(Salazar *et al.* 2008)	SN	↑ levels in TH neurons
Fe (Total)	(Oakley *et al.* 2007),(Jellinger *et al.* 1992),(Good *et al.* 1992)	SN	↑ levels in TH neurons
Fe (Total)	(Dexter *et al.* 1989),(Ayton *et al.* 2013),(Hirsch *et al.* 1991),(Riederer *et al.* 1989)	SN	↑ levels
Fe (Total)	(Dexter *et al.* 1989)	GP	↓ levels
Fe (Total)	(Dexter *et al.* 1989),(Ayton *et al.* 2013),(Riederer *et al.* 1989)	Ca, Cb, Cx, GP, Hp, Pu	= levels
Fe^{2+}	(Riederer *et al.* 1989)	Cx, GP, Hp, Pu, SN	= levels
Fe^{3+}	(Riederer *et al.* 1989)	SN	↑ levels
Fe^{3+}	(Riederer *et al.* 1989)	Cx, GP, Hp, Pu	= levels
Ferritin	(Riederer *et al.* 1989)	SN	↑ levels
Ferritin	(Riederer *et al.* 1989)	Pu	= levels
Ferritin (H-Chain)	(Galazka-Friedman *et al.* 2004)	SN	= levels
Ferritin (L-Chain)	(Galazka-Friedman *et al.* 2004)	SN	↓ levels
Ferroportin	(Visanji *et al.* 2013)	SN	↑ levels
Lactoferrin	(Rousseau *et al.* 2013),(Leveugle *et al.* 1996)	SN	↑ levels in TH neurons
Lactoferrin receptor	(Faucheux *et al.* 1995)	SN	↑ levels in TH neurons
Metallothionein 1 and 2	(Michael *et al.* 2011)	SN	↑ nb of expressing astrocytes
Mg (Total)	(Riederer *et al.* 1989)	Ca, GP, Pu, Rp, SN	= levels
Mn (Total)	(Dexter *et al.* 1989)	Pu	↓ levels
Mn (Total)	(Dexter *et al.* 1989)	Ca, Cb, Cx, GP, SN	= levels

NDFIP1	(Howitt *et al.* 2014)	SN	↑ levels
Pb (Total)	(Dexter *et al.* 1989)	Ca, Cb, Cx, GP, Pu, SN	= levels
Transferrin	(Mastroberardino *et al.* 2009)	SN	↑ levels
Transferrin	(Faucheux *et al.* 1997)	SN	↓ levels in TH neurons
Transferrin receptor	(Mash *et al.* 1991)	Pu	↓ levels
Transferrin receptor	(Mash *et al.* 1991)	Ca, GP	= levels
Zn (Total)	(Dexter *et al.* 1989),(Riederer *et al.* 1989)	Ca, Pu, Rp, SN	↑ levels
Zn (Total)	(Dexter *et al.* 1989),(Riederer *et al.* 1989)	Ca, Cb, Cx, GP, Pu, SN	= levels

Calcium and calcium-binding proteins			
Ca^{2+} (Total)	(Riederer *et al.* 1989)	Ca, GP, Pu, Rp, SN	= levels
Calbindin	(Hurley *et al.* 2013)	NBM, SN	↓ nb of expressing cells
Calbindin	(Hurley *et al.* 2013)	Cb Cx, LC	= levels
Calcium channels	(Watson *et al.* 1988)	Str	= levels
Calmodulin	(Hurley *et al.* 2013),(Reynolds *et al.* 2008)	Cb Cx, LC, SN	↓ nb of expressing cells
Calmodulin	(Hurley *et al.* 2013)	NuBa	= levels
Calpain II	(Mouatt-Prigent *et al.* 1996)	LC, SN	↑ nb of expressing neurons
Calpastatin	(Mouatt-Prigent *et al.* 2000)	SN	↓ nb TH neurons
Calreticulin	(Hurley *et al.* 2013)	LC, NBM, SN	↓ nb of expressing cells
Calreticulin	(Hurley *et al.* 2013)	Cb Cx	= levels
Calreticulin	(Wilhelmus *et al.* 2011b)	SN	↑ levels in TH neurons
$Ca_v1.2$	(Hurley *et al.* 2013)	LC, NBM, SN	↓ nb of expressing cells
$Ca_v1.2$	(Hurley *et al.* 2013)	Cb Cx	= levels
$Ca_v1.3$	(Hurley *et al.* 2013)	Cb Cx, LC	↑ nb of expressing cells
$Ca_v1.3$	(Hurley *et al.* 2013)	NBM, SN	↓ nb of expressing cells
Lipocortin-1	(Knott *et al.* 2000)	SN	↑ levels in microglial cells
Parvalbumin	(Soós *et al.* 2004)	SN	↑ levels in TH neurons
PKC	(Tanaka *et al.* 1993)	SN	↓ levels

Table 4. Changes in neuroinflammatory-related proteins observed in the human parkinsonian brain. Legend: see Table 1.

Protein	Ref	Structure	Observation in PD
C1q+ microglia	(Depboylu *et al.* 2011)	SN	↑ nb
C9	(Loeffler *et al.* 2006)	SN	= levels
Caspase-3 (activated)	(Burguillos *et al.* 2011)	SN	↑ levels in microglia
Caspase-8 (activated)	(Burguillos *et al.* 2011)	SN	↑ levels in microglia
CCL5	(Shimoji *et al.* 2009)	Str	↓ levels
CCL5	(Shimoji *et al.* 2009)	Fr Cx, SN	= levels
CD163	(Pey *et al.* 2014)	LC, SN	↑ nb of expressing microglia
CD23	(Hunot *et al.* 1999)	SN	↑ levels
CD23	(Hunot *et al.* 1999)	SN	↑ nb of expressing microglia
CD23	(Hunot *et al.* 1999)	SN	↑ nb of expressing astrocyte
CD68+ microglia	(Vroon *et al.* 2007)	OB	↑ nb
CD4+ T cells	(Brochard *et al.* 2009)	SN	↑ nb
CD8+ T cells	(Brochard *et al.* 2009)	SN	↑ nb
CR3/43+ microglia	(Imamura *et al.* 2003),(Imamura *et al.* 2005),(Orr *et al.* 2005)	Cg Cx, Hp, Pu,SN	↑ nb
CXCL12	(Shimoji *et al.* 2009)	Str	↑ levels
CXCL12	(Shimoji *et al.* 2009)	Fr Cx, SN	= levels
CXCR4	(Shimoji *et al.* 2009)	SN, Str	↑ levels
CXCR4	(Shimoji *et al.* 2009)	LC	= levels
Cyclooxygenase-2	(Teismann *et al.* 2003)	SN	↑ levels in TH neurons
Cyclooxygenase-2	(Teismann *et al.* 2003)	SN	↑ levels
GFAP	(Lastres-Becker *et al.* 2012),(Mythri *et al.* 2011)	Ca, Fr Cx, SN	↑ levels
GFAP	(Mythri *et al.* 2011)	Pu	= levels
Glucocorticoid receptors	(Ros-Bernal *et al.* 2011)	Pu	↑ levels
HO-1	(Schipper *et al.* 2009)	SN	↑ nb of expressing astrocytes
Iba1	(Lastres-Becker *et al.* 2012)	SN	↑ levels
iC3b	(Loeffler *et al.* 2006)	SN	↑ nb of expressing TH cells
ICAM-1+astrocytes	(Miklossy *et al.* 2006)	SN	↑ nb
ICAM-1+ microglia	(Imamura *et al.* 2003)	Hp, Pu, SN	↑ nb
IgG	(Orr *et al.* 2005)	SN	↑ levels in TH neurons
IL-1β	(Mogi *et al.* 1994a)	Ca, Pu	↑ levels
IL-1β	(Mogi *et al.* 1994a)	Cb Cx	= levels
IL-1β	(Hunot *et al.* 1999)	SN	↑ nb of expressing glial cells
IL-2	(Mogi *et al.* 1996b)	Ca, Pu	↑ levels
IL-2	(Mogi *et al.* 1996b)	Cx	= levels
IL-6	(Mogi *et al.* 1994a)	Ca, Pu	↑ levels

IL-6	(Mogi *et al.* 1994a)	Cb Cx	= levels
iNOS	(Knott *et al.* 2000)	SN	↑ levels in glial cells
Interferon ɣ	(Hunot *et al.* 1999)	SN	↑ nb of expressing glial cells
Interferon-ɣ	(Mogi *et al.* 2007)	Ca, Pu, SN	↑ levels
Interferon-ɣ	(Mogi *et al.* 2007)	Cb, Fr Cx	= levels
Interferon-ɣ receptor	(Hashioka *et al.* 2009)	SN	↑ levels in astrocytes
Ki-M1p+ microglia	(Imamura *et al.* 2005)	SN	↑ nb
LFA-1+ leukocyte	(Miklossy *et al.* 2006)	SN	↑ nb
LFA-1+ microglia	(Miklossy *et al.* 2006)	SN	↑ nb
Lipocortin-1	(Knott *et al.* 2000)	SN	↑ levels in microglial cells
MFGE8	(Kinugawa *et al.* 2013)	SN	↑ expression in astrocytes
Myeloperoxidase	(Choi *et al.* 2005a)	SN	↑ levels in astrocytes
NF-κB (nuclear)	(Soós *et al.* 2004)	SN	↑ levels in TH neurons nuclei
NOS	(Hunot *et al.* 1996)	SN, VTA	↑ nb of expressing glial cells
NOS	(Hunot *et al.* 1996)	SN, VTA	↓ nb of expressing neurons
RAGE	(Sathe *et al.* 2012)	Mb	= levels
S100B	(Sathe *et al.* 2012)	Mb	↑ levels in astrocytes
TNF-α	(Hunot *et al.* 1999)	SN	↑ nb of expressing glial cells
TNF-α	(Mogi *et al.* 1994b)	Ca, Str	↑ levels

Table 5. Changes in mitochondrial and oxidative stress-related proteins observed in the human parkinsonian brain. Legend: see Table 1.

Protein	Ref	Structure	Observation in PD
Mitochondrial abnormalities and energy deficit			
6PGD	(Dunn *et al.* 2014)	Cx, Pu	↓ levels and activity
AF6	(Haskin *et al.* 2013)	SN, Str	↓ levels
ATP synthase	(Ferrer *et al.* 2007)	SN	↓ levels
ATP synthase	(Ferrer *et al.* 2007)	Fr Cx	↑ levels
Citrate synthase	(Schapira *et al.* 1990)	Ca, Cb, Cr Cx, GP, SN	= activity
Complex I	(Moisoi *et al.* 2009)	Mb	↓ levels
Complex I	(Keeney *et al.* 2006)	Fr Cx	= levels
Complex I	(Hattori *et al.* 1993)	SN	↓ nb of expressing neurons
Complex I	(Navarro *et al.* 2009),(Schapira *et al.* 1990),(Schapira *et al.* 1989),(Keeney *et al.* 2006),(Parker *et al.* 2008)	Fr Cx, SN	↓ activity
Complex I	(Mythri *et al.* 2011),(Schapira *et al.* 1990)	Ca, Cb, Cr Cx, Fr Cx, GP, Pu	= activity
Complex I (carbonylated)	(Keeney *et al.* 2006)	Fr Cx	↑ levels
Complex II	(Moisoi *et al.* 2009)	Mb	↓ levels
Complex II	(Keeney *et al.* 2006)	Fr Cx	= levels
Complex II	(Navarro *et al.* 2009),(Parker *et al.* 2008)	Fr Cx	= activity
Complex III	(Keeney *et al.* 2006)	Fr Cx	= levels
Complex III	(Schapira *et al.* 1990),(Parker *et al.* 2008)	Ca, Cb, Cr Cx, Fr Cx, GP, SN	= activity
Complex III	(Moisoi *et al.* 2009)	Mb	↓ levels
Complex IV	(Moisoi *et al.* 2009),(Itoh *et al.* 1997)	Mb, SN	↓ levels
Complex IV	(Keeney *et al.* 2006)	Fr Cx	= levels
Complex IV	(Navarro *et al.* 2009),(Schapira *et al.* 1990),(Parker *et al.* 2008)	Ca, Cb, Cr Cx, Fr Cx, GP, SN	= activity
Complex V	(Keeney *et al.* 2006)	Fr Cx	= levels
Complex V α	(Moisoi *et al.* 2009)	Mb	↓ levels
Cytochrome a	(Navarro *et al.* 2009)	Fr Cx	= levels
Cytochrome b	(Navarro *et al.* 2009)	Fr Cx	↑ levels
Cytochrome c	(Navarro *et al.* 2009)	Fr Cx	↑ levels
DNA damage (mitochondria)	(Sanders *et al.* 2014)	SN	↑ nb in TH neurons
DNA deletion (mitochondria)	(Bender *et al.* 2006)	SN	↑ levels
DNA deletion (mitochondria)	(Bender *et al.* 2006)	Hp	= levels
DNA mutation (mitochondria)	(Lin *et al.* 2013)	SN	↑ nb in neurons
G6PD	(Dunn *et al.* 2014)	Cx, Pu	↓ levels and activity
Hemoglobin (alpha and beta)	(Shephard *et al.* 2014)	SN	↓ levels

HtrA2 (P-S142)	(Plun-Favreau *et al.* 2007)	Ca	↑ levels
mitochondrial oxidative damage	(Navarro *et al.* 2009)	Fr Cx	↑ levels
mitochondrial oxygen uptake	(Navarro *et al.* 2009)	Fr Cx	↓ levels
NADPH production	(Dunn *et al.* 2014)	Cx, Pu	↑ levels
ND6	(She *et al.* 2011)	Str	↓ mitochondrial levels
Nicotinamide N-methyltransferase	(Parsons *et al.* 2003)	Ca, Cb	↑ levels and activity
NOS (mitochondrial)	(Navarro *et al.* 2009)	Fr Cx	↑ activity
oxygen uptake	(Navarro *et al.* 2009)	Fr Cx	↓ levels
Prohibitin	(Ferrer *et al.* 2007)	SN	↓ levels
Prohibitin	(Ferrer *et al.* 2007)	Fr Cx	↑ levels
TOM20	(Bender *et al.* 2013)	Mb	= levels
TOM40	(Bender *et al.* 2013)	Mb	↓ levels
VDAC1	(Chu *et al.* 2014)	SN	↓ nb of expressing TH neurons
α-ketoglutarate dehydrogenase	(Mizuno *et al.* 1994)	SN	↓ levels
Oxidative stress			
4-hydroxynonenal	(Yoritaka *et al.* 1996)	SN	↑ nb of reactive cells
Ascorbic acid (total)	(Riederer *et al.* 1989)	Ca, GP, Pu, Ra, SN	= levels
ATM (phosphorylated at S1981)	(Camins *et al.* 2010)	Cg Cx	↑ levels
Biliverdin reductase	(Reynolds *et al.* 2008)	SN	↑ levels
Catalase	(Ambani *et al.* 1975)	SN, Str	↓ activity
Catalase	(Mythri *et al.* 2011)	Ca, Fr Cx, Pu	= activity
Creatine kinase	(Aksenova *et al.* 1999)	Fr Cx	= activity
DNA polymerase δ	(Camins *et al.* 2010)	Cg Cx	↑ levels
ɣ-glutamyl cysteine ligase (ɣ-GCL)	(Mythri *et al.* 2011)	Ca, Fr Cx, Pu	= activity
ɣ-glutamyl transpeptidase (ɣGT)	(Mythri *et al.* 2011)	Ca, Fr Cx, Pu	↓ activity
ɣ-glutamylcysteine synthetase	(Sian *et al.* 1994)	Ca, Cr Cx, GP, Pu, SN	= activity
ɣ-glutamyltranspeptidase	(Sian *et al.* 1994)	Ca, Cr Cx, GP, Pu, SN	= activity
ɣ-H2AX (phosphorylated)	(Camins *et al.* 2010)	Cg Cx	↑ levels
Glutathione (oxidized)	(Sian *et al.* 1994)	Cr Cx, Pu, SN	= levels
Glutathione (oxidized)	(Sofic *et al.* 1992)	SN	↓ levels
Glutathione (reduced)	(Pearce *et al.* 1997)	SN	↓ levels in TH neurons
Glutathione (reduced)	(Sian *et al.* 1994)	SN	↓ levels
Glutathione (reduced)	(Sian *et al.* 1994)	Cr Cx, Pu, SN	= levels
Glutathione (reduced)	(Mythri *et al.* 2011)	Ca, Fr Cx, Pu	↑ activity
Glutathione Peroxidase (GPx)	(Power *et al.* 2002)	Fr Cx	↑ nb of expressing astrocytes
Glutathione Peroxidase (GPx)	(Mythri *et al.* 2011),(Sian *et al.* 1994)	Ca, Cr Cx, Fr Cx, GP, Pu, SN	= activity
Glutathione Peroxidase (GPx)	(Mythri *et al.* 2011)	Ca, Pu	↑ activity

Glutathione Peroxidase (GPx)	(Power *et al.* 2002)	Cg Gy, Fr Gy	↑ levels in microglia
Glutathione reductase (GR)	(Mythri *et al.* 2011)	Ca, Fr Cx, Pu	= activity
Glutathione-S-tranferase (GST)	(Mythri *et al.* 2011)	Ca, Fr Cx, Pu	= activity
Glutathione-S-tranferase (GST)	(Reynolds *et al.* 2008)	SN	↓ levels
Gluthatione transferase	(Sian *et al.* 1994)	Ca, Cr Cx, GP, Pu, SN	= activity
HO1	(Schipper 2004)	SN	↑ nb of expressing astrocytes
HO1	(Lastres-Becker *et al.* 2012)	SN	↑ levels
Lipid peroxydation	(Mythri *et al.* 2011)	Fr Cx	↑ levels
Lipid peroxydation	(Mythri *et al.* 2011)	Ca, Pu	↓ levels
Mitochondrial oxidative damage	(Navarro *et al.* 2009)	Fr Cx	↑ levels
Mitochondrial proteins	(Navarro *et al.* 2009)	Fr Cx	↑ levels
MTH1	(Nakabeppu *et al.* 2007)	SN	↑ levels
MTH1	(Shimura-Miura *et al.* 1999)	SN	↑ levels in mitochondria
MUTYH	(Nakabeppu *et al.* 2007)	SN	↑ levels
MUTYH	(Arai *et al.* 2006)	SN	↑ levels in TH neurons
NOX1	(Choi *et al.* 2012)	SN	↑ nb of TH neurons
NQO1 (NADPH quinone oxidoreductase)	(van Muiswinkel *et al.* 2004)	SN	↑ levels in neurons and astrocytes
Nrf2	(Ramsey *et al.* 2007)	SN	↑ nuclear and ↓cytoplasmic levels
Nucleolar integrity	(Rieker *et al.* 2011)	SN	↓levels in TH neurons
OGG1	(Shimura-Miura *et al.* 1999)	SN	↑ total and mitochondrial levels
Osteopontin	(Maetzler *et al.* 2007)	SN	↑ levels
Osteopontin	(Iczkiewicz *et al.* 2006)	SN	↓ nb of positive cells
PARP	(Soós *et al.* 2004)	SN	↑ levels in TH nuclei
Peroxidase	(Ambani *et al.* 1975)	SN, Str	↓ activity
Peroxiredoxin 2 (phosphorylated at T89)	(Qu *et al.* 2007)	SN	↑ levels in TH neurons
Peroxiredoxin 2 (S-nytrosylated)	(Fang *et al.* 2007)	SN	↑ levels
Peroxiredoxin 3 (phosphorylated)	(Angeles *et al.* 2011)	Ca, Cx	↑ levels
Selenoprotein P	(Bellinger *et al.* 2012)	SN	↓ total but ↑ levels in TH neuron
Sestrin-2	(Zhou *et al.* 2013)	SN	↑ levels
SOD	(Marttila *et al.* 1988)	NBM, SN, Th, Tp Cx	↑ activity
SOD	(Marttila *et al.* 1988)	Ag, Ca, Cb, GP, Pu	= levels
SOD	(Mythri *et al.* 2011),(Marttila *et al.* 1988)	Ca, Fr Cx	= activity
SOD	(Mythri *et al.* 2011)	Pu	↓ activity
SOD (cytosolic)	(Radunović *et al.* 1997)	Cx	= activity
SOD (mitochondrial)	(Radunović *et al.* 1997)	Cx	↑ activity

SOD (Mn)	(Shimoda-Matsubayashi *et al.* 1997)	Fr Cx, Pu, SN	= activity
SOD (Mn)	(Navarro *et al.* 2009)	Frontal cortex	↑ levels
SOD1	(Choi *et al.* 2005b)	Cg Cx	↑ levels
SOD2	(Ferrer *et al.* 2007)	SN	↑ levels
Thioredoxin	(Reynolds *et al.* 2008)	SN	= levels
Total proteins (carbonylated)		Fr Cx	= levels
Total proteins (carbonylated)	(Alam *et al.* 1997)	Ca, Cb, Fr Cx, GP, Nacc, Pu, SN	↑ levels
Total proteins (carbonylated)	(Aksenova *et al.* 1999)	Fr Cx	= levels
Total proteins (oxidized)	(Mythri *et al.* 2011),(Choi *et al.* 2005b)	Ca, Cg Cx	↑ levels
Total proteins (oxidized)	(Mythri *et al.* 2011)	Fr Cx, Pu	= levels
Total proteins (nitrosylated)	(Mythri *et al.* 2011)	Ca, Fr Cx, Pu	= levels
TTRAP (cytoplasmic)	(Vilotti *et al.* 2012)	SN	↑ in TH neurons

Table 6. Changes in ubiquitin proteasome system, lysosomal and autophagy proteins observed in the human parkinsonian brain. Legend: see Table 1.

Protein	Ref	Structure	Observation in PD
Ubiquitin proteasome system			
19S proteasome	(Wills *et al.* 2010)	Fr Gy, Str	= levels
20S proteasome	(Wills *et al.* 2010)	Fr Gy, Str	↓ levels
20S proteasome	(Chu *et al.* 2009)	SN	↓ levels in neurons
20S proteasome (α subunit)	(McNaught *et al.* 2003)	SN	↓ levels
20S proteasome (α6 subunit)	(Nakamura *et al.* 2006)	Str	↑ levels and nuclear localization
20S proteasome (α6 subunit)	(Nakamura *et al.* 2006)	SN	↑ levels
20S proteasome	(McNaught and Jenner 2001)	SN	↓ activity
20S proteasome	(McNaught and Jenner 2001)	Cb, Fr Cx, Hp, Po, Str	= activity
20S/26S proteasome	(McNaught and Jenner 2001)	SN	↓ activity
20S (α4 subunit)	(Bukhatwa *et al.* 2010)	SN	↓ nb of expressing TH neurons
20S (α6 subunit)	(Bukhatwa *et al.* 2010)	SN	↓ nb of expressing TH neurons
20S (β3 subunit)	(Bukhatwa *et al.* 2010)	SN	= levels
20S (β5 subunit)	(Bukhatwa *et al.* 2010)	SN	= levels
26S proteasome	(Wills *et al.* 2010)	Str	= activity
26S proteasome	(Wills *et al.* 2010)	Fr Gy	↓ activity
26S/20S proteasome (α subunit)	(McNaught *et al.* 2003)	Fr Cx, Str	= levels
26S/20S proteasome (α subunit)	(McNaught *et al.* 2003)	SN	↓ levels
26S/20S proteasome (β subunit)	(McNaught *et al.* 2003)	Fr Cx, SN, Str	= levels
Nedd4	(Tofaris *et al.* 2011)	SN	↑ cytoplasmic levels in TH neurons
PA28	(McNaught *et al.* 2003)	Fr Cx	↓ levels
PA28	(McNaught *et al.* 2003)	SN, Str	= levels
PA700	(McNaught *et al.* 2003)	Fr Cx, SN, Str	↑ levels
SKP1A	(Mandel *et al.* 2007)	SN	↓ levels
TRIM9	(Tanji *et al.* 2010)	SN	↓ levels
Ubiquitinated proteins	(Lonskaya *et al.* 2013)	Str	↑ levels
USP9X	(Rott *et al.* 2011)	SN	↓ levels
Lysosome and autophagy			
Beclin 1	(Murphy *et al.* 2014)	Cg Cx	↓ levels
Beclin 1	(Miki *et al.* 2015)	SN	↑ levels
Beclin 1 (caspase-cleaved)	(Rohn and Catlin 2011)	SN	↑ levels
Beclin1 (phosphorylated)	(Miki *et al.* 2015)	SN	= levels
Cathepsin A	(Murphy *et al.* 2014)	Cg Cx	↑ levels
cathepsin B	(Mantle *et al.* 1995)	Fr Cx	= levels
Cathepsin D	(Murphy *et al.* 2014)	Cg Cx	↑ levels

Cathepsin D	(Chu *et al.* 2009)	SNc	↓ levels in neurons
cathepsin D	(Mantle *et al.* 1995)	Fr Cx	= levels
cathepsin H	(Mantle *et al.* 1995)	Fr Cx	= levels
cathepsin L	(Mantle *et al.* 1995)	Fr Cx	= levels
Dipeptidyl aminopeptidase I	(Mantle *et al.* 1996)	Fr Cx	= activity
Dipeptidyl aminopeptidase II	(Mantle *et al.* 1996)	Fr Cx	↓ activity
Glucocerebrosidase	(Murphy *et al.* 2014)	Cg Cx	↓ levels
Glucocerebrosidase	(Gegg *et al.* 2012)	Crb	↓ levels and activity
Glucocerebrosidase	(Gegg *et al.* 2012)	SN	↓ levels and activity
Glucocerebrosidase	(Gegg *et al.* 2012)	Ag, Fr Cx, Pu	= levels
Hsc70	(Alvarez-Erviti *et al.* 2010),(Mandel *et al.* 2009)	Ag, SN	↓ levels
HSP73	(Chu *et al.* 2009)	SN	↓ levels in neurons
LAMP1	(Dehay *et al.* 2010)	SN	↓ levels
LAMP1	(Chu *et al.* 2009)	SN	↓ levels in neurons
LAMP2	(Alvarez-Erviti *et al.* 2010),(Murphy *et al.* 2014)	Ag, Cg Cx, SN	↓ levels
LC3II	(Dehay *et al.* 2010)	SN	↑ levels
LIMP-2	(Rothaug *et al.* 2014)	SN	↑ levels
LMX1B	(Laguna *et al.* 2015)	SN	↓ levels in TH neurons
MEF2D	(She *et al.* 2011)	Str	↑ levels
P-type ATPase (ATP13A2)	(Dehay *et al.* 2012)	SN	↓ levels
P-type ATPase (ATP13A2)	(Ramonet *et al.* 2012)	Cx, Str	↑ levels
TFEB	(Decressac *et al.* 2013)	SN	↓ nuclear levels in TH neurons
ULK1 (UNC-51-like kinase 1)	(Miki *et al.* 2015)	SN	= levels
ULK2 (UNC-51-like kinase 2)	(Miki *et al.* 2015)	SN	= levels
VPS34	(Miki *et al.* 2015)	SN	= levels

Table 7. Changes in apoptosis-related proteins observed in the human parkinsonian brain.
Legend: see Table 1.

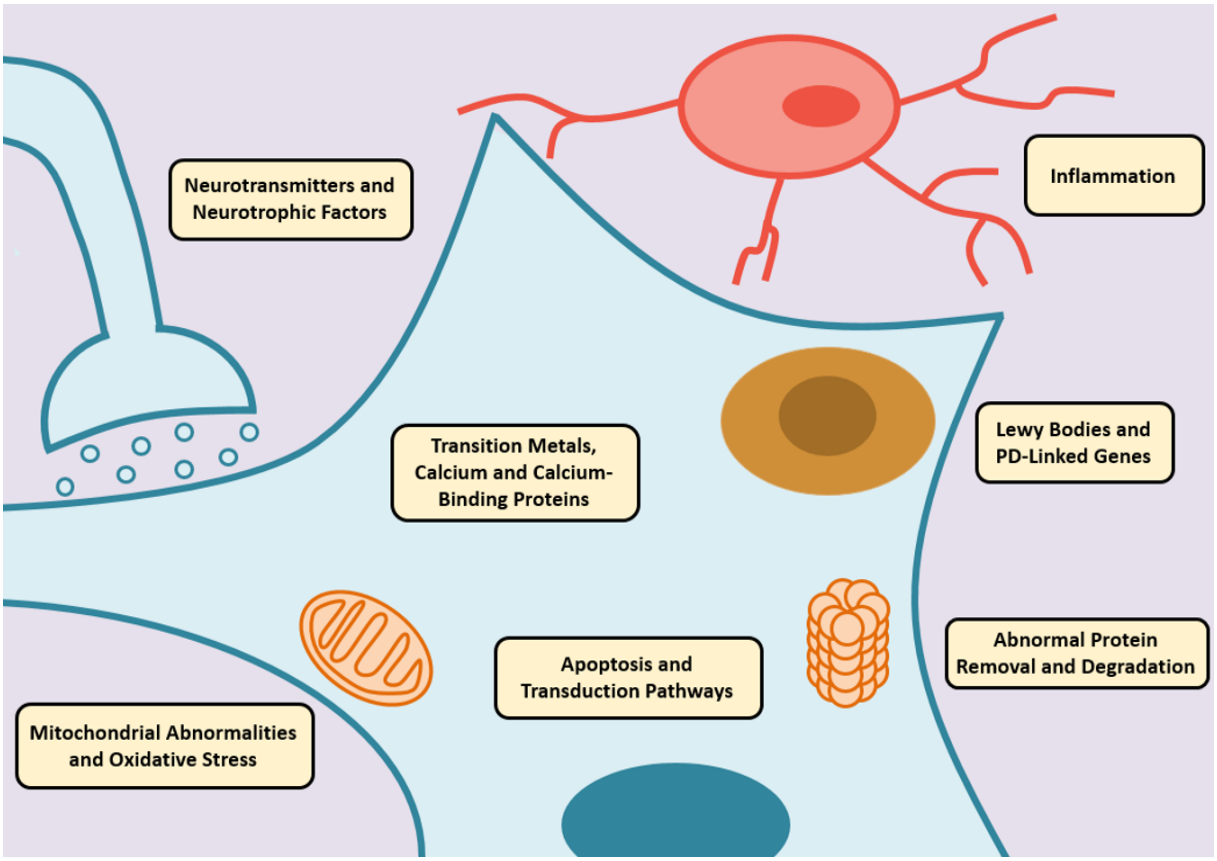
Protein	Ref	Structure	Effect
Apoptosis			
AIMP2	(Lee *et al.* 2013)	SN	↑ levels
Apaf-1	(Kawamoto *et al.* 2014)	SN	↑ levels in TH neurons
Apaf-1	(Kawamoto *et al.* 2014)	LC	↑ levels
Bax	(Tatton 2000),(Hartmann *et al.* 2001a)	SN	↑ levels in TH neurons
Bcl-2	(Letters *et al.* 1996),(Marshall *et al.* 1997)	Ca, GP, Pu, SN	↑ levels
Bcl-2	(Letters *et al.* 1996),(Marshall *et al.* 1997)	Cb Cx, Cx	= levels
Bid/tBid	(Jiang *et al.* 2012)	Tp Cx	↑ total and mitochondrial levels
Caspase-1	(Mogi *et al.* 2000)	SN	↑ activity
Caspase-1	(Mogi *et al.* 2000)	Ca, Cb, Fr Cx, Pu	= activity
Caspase-3	(Hartmann *et al.* 2000)	SN	↓ nb of expressing TH neurons
Caspase-3	(Jiang *et al.* 2012)	Tp Cx	↑ total and mitochondrial levels
Caspase-3	(Tatton 2000),(Mogi *et al.* 2000)	SN	↑ levels in TH neurons and activity
Caspase-3	(Mogi *et al.* 2000)	Ca, Cb, Fr Cx, Pu	= activity
Caspase-3 (cleaved)	(Jiang *et al.* 2012)	Tp Cx	↑ total and mitochondrial levels
Caspase-3 (cleaved)	(Tatton 2000)	SN	↑ levels in TH neurons
Caspase-8 (activated)	(Viswanath *et al.* 2001)	SN	↑ levels in TH neurons
Caspase-8 (activated)	(Hartmann *et al.* 2001b)	SN	↑ nb of TH expressing neurons
Caspase-9	(Kawamoto *et al.* 2014)	SN	↑ levels in TH neurons
Caspase-9	(Kawamoto *et al.* 2014)	LC	↑ levels
Caspase-9 (activated)	(Viswanath *et al.* 2001)	SN	↑ levels in TH neurons
Caspase-9 (cleaved)	(Kawamoto *et al.* 2014)	SN	↑ levels in TH neurons
Caspase-9 (cleaved)	(Kawamoto *et al.* 2014)	LC	↑ levels
Cytochrome c	(Kawamoto *et al.* 2014)	SN	↑ levels in TH neurons
Cytochrome c	(Kawamoto *et al.* 2014)	LC	↑ levels
Cytochrome c	(Jiang *et al.* 2012)	Tp Cx	↑ total and ↓ mitochondrial levels
Endonuclease G	(Büttner *et al.* 2013)	SN	↑ nuclear localization in TH neurons
FADD	(Hartmann *et al.* 2002)	SN	↓ nb of expressing neurons
Fas	(Ferrer *et al.* 2000)	SN	↓ levels
Fas (soluble)	(Mogi *et al.* 1996a)	Ca, Pu	↑ levels
Fas (soluble)	(Mogi *et al.* 1996a)	Cb Cx	= levels
Fas-associated factor 1	(Betarbet *et al.* 2008)	Fr Cx	↑ levels
FasL	(Ferrer *et al.* 2000)	SN	↓ levels in TH neurons

FasL	(Ferrer *et al.* 2000)	SN	↑ levels in reactive astrocytes
p53	(Sunico *et al.* 2013),(Mogi *et al.* 2007)	Ca, Tp Cx	↑ levels
p53	(Mogi *et al.* 2007)	Cb, Fr Cx, Pu, SN	= levels
p53 (phosphorylated at S15)	(Camins *et al.* 2010)	Cg Gy	↑ levels
PAR polymer	(Lee *et al.* 2013)	SN	↑ levels
Par-4	(Moos and Jensen 2004)	SN	= levels
TNFR1 (p55)	(Jiang *et al.* 2012),(Mogi *et al.* 2000)	SN, Tp Cx	↑ levels
TNFR1 (p55)	(Mogi *et al.* 2000)	Ca, Cb, Fr Cx, Pu	= levels
TRADD	(Jiang *et al.* 2012)	Tp Cx	↑ levels

Cell cycle re-entry			
Cdk5	(Alvira *et al.* 2008)	Cg Cx	↑ levels
Cdk5	(Rubio de la Torre *et al.* 2009)	Ca, Cb, Cx	= levels
Cyclin D1	(Camins *et al.* 2010)	Cg Cx	↑ levels
E2F-1	(Alvira *et al.* 2008)	Cg Cx	↑ levels
E2F-1	(Höglinger *et al.* 2004)	SN	↑ levels in TH neurons
p25	(Rubio de la Torre *et al.* 2009),(Alvira *et al.* 2008)	Ca, Cg Cx	↑ levels
p25	(Rubio de la Torre *et al.* 2009)	Cb, Cx	= levels
p35	(Rubio de la Torre *et al.* 2009)	Ca, Cb, Cx	= levels
PCNA	(Höglinger *et al.* 2004)	SN	↑ levels in TH neurons
pRb	(Jordan-Sciutto *et al.* 2003)	Fr Cx, Hp, SN	↑ levels
pRb (phosphorylated)	(Jordan-Sciutto *et al.* 2003)	Fr Cx, Hp, SN	↑ nuclear levels
Endoplasmic reticulum stress			
EIF2α (phosphorylated at S51)	(Hoozemans *et al.* 2007)	SN	↑ nb of expressing TH neurons
HERP	(Slodzinski *et al.* 2009)	SN	↑ levels
IRE1α	(Hoozemans *et al.* 2012)	SN	↑ nb of expressing TH neurons
PERK (phosphorylated at Thr981)	(Hoozemans *et al.* 2007)	SN	↑ nb of expressing TH neurons
PKR (phosphorylated at Thr446)	(Bando *et al.* 2005)	Hp	↑ nuclear levels
Transcription factors and transduction pathways			
14-3-3 (phosphorylated at S58)	(Slone *et al.* 2015)	Tp Cx	↓ membrane levels
14-3-3 (total pan)	(Slone *et al.* 2015)	Tp Cx	= levels
14-3-3ɵ (phosphorylated at S232)	(Slone *et al.* 2015)	Tp Cx	↑ cytoplasmic levels
14-3-3σ	(Reynolds *et al.* 2008)	SN	↑ levels
Akt (phosphorylated at S473)	(Timmons *et al.* 2009)	Mb	↓ levels
Akt (phosphorylated at S473)	(Malagelada *et al.* 2008)	SN	↓ levels in TH neurons

Akt (phosphorylated at T308)	(Malagelada *et al.* 2008)	SN	↓ levels in TH neurons
Akt (total)	(Timmons *et al.* 2009)	Mb	↓ levels
ASK1 (phosphorylated)	(Hu *et al.* 2011)	SN	↑ nb of expressing TH neurons
c-jun	(Hunot *et al.* 2004)	SN	↑ levels in TH neurons
c-Myc	(Ferrer and Blanco 2000)	SN	= levels in TH neurons
c-Myc	(Ferrer and Blanco 2000)	SN	↑ nb of expressing astrocytes
CREB (phosphorylated)	(Kurup *et al.* 2015)	Str	↓ levels
CREB (phosphorylated)/CREB	(Price *et al.* 2010)	Fr Cx	↑ nuclear and ↓ cytoplasmic levels
Elk (phosphorylated)/Elk	(Price *et al.* 2010)	Fr Cx	= ratio
ERK (phosphorylated)/ERK	(Price *et al.* 2010)	Fr Cx	↑ ratio
ERK1/2 (phosphorylated)	(Kurup *et al.* 2015)	Str	↓ levels
GSK3β (phosphorylated at Y216)	(Wills *et al.* 2010)	Str	↑ levels
GSK3β (phosphorylated at Y216)	(Wills *et al.* 2010)	Fr Cx	= levels
Itch	(Pranski *et al.* 2013)	Cx, SN	= levels
JNK (phosphorylated)	(Hu *et al.* 2011)	SN	↑ nb of expressing TH neurons
MEF2D	(Gao *et al.* 2014)	Str	↓ mitochondrial levels
MEF2D	(Chu *et al.* 2011)	SN	↓ levels
MEF2D	(Chu *et al.* 2011)	SN	↓ levels in TH neurons
NFATc4	(Caraveo *et al.* 2014)	Fr Cx, Hp, SN	↑ nuclear levels
NF-κB (nuclear)	(Soós *et al.* 2004)·(Hunot *et al.* 1997)	SN	↑ levels in TH neurons
NF-κB (p50), cytosol	(Reynolds *et al.* 2008)	SN	↑ cytosolic and nuclear levels
NF-κB (p65)	(Reynolds *et al.* 2008)·(Ghosh *et al.* 2009)	Mb	↑ total, cytosolic and nuclear levels
NF-κB (phosphorylated at S536)	(Reynolds *et al.* 2008)	SN	↑ levels
NF-κB (total)	(Mogi *et al.* 2007)	Ca, Pu, SN	↑ levels
n-myc	(Ferrer and Blanco 2000)	SN	= levels in TH neurons
n-myc	(Ferrer and Blanco 2000)	SN	↑ nb of expressing astrocytes
Nurr1	(Chu *et al.* 2006)	SN	↓ levels in TH neurons
Nurr1	(Chu *et al.* 2006)	SN	↓ nb of expressing TH neurons
p38 (phosphorylated)	(Hu *et al.* 2011)	SN	↑ nb of expressing TH neurons
p53	(Sunico *et al.* 2013)·(Mogi *et al.* 2007)	Ca, Tp Cx	↑ levels
p53	(Mogi *et al.* 2007)	Cb, Fr Cx, Pu, SN	= levels
p53 (phosphorylated at S15)	(Camins *et al.* 2010)	Cg Gy	↑ levels
PGC-1α	(Eschbach *et al.* 2015; Shin *et al.* 2011)	SN, Str	↓ levels
PTEN (S-nytrosylated)	(Choi *et al.* 2014)	Fr Cx	↓ ratio / total DJ-1
RNF11	(Pranski *et al.* 2013)	Cx, SN	↓ levels
RPT801 (REDD1)	(Malagelada *et al.* 2006)	SN	↑ levels in TH neurons
Tax1BP1	(Pranski *et al.* 2013)	Cx, SN	= levels

Summarizing Schematic



Parkinson's is accompanied by multiple changes in the brain that are responsible of the progression of the disease. We describe here the molecular alterations occurring in postmortem brains and classify them as: Neurotransmitters and neurotrophic factors; Lewy bodies and Parkinson's-linked genes; Transition metals, calcium and calcium-binding proteins; Inflammation; Mitochondrial abnormalities and oxidative stress; Abnormal protein removal and degradation; Apoptosis and transduction pathways.