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5-S-cysteinyl-dopamine, a neurotoxic endogenous metabolite of dopamine: Implications for Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide and is characterized for being an idiopathic and multifactorial disease. Extensive research has been conducted to explain the origin of the disease, but it still remains elusive. It is well known that dopamine oxidation, through the endogenous formation of toxic metabolites, is a key process in the activation of a cascade of molecular events that leads to cellular death in the hallmark of PD. Thio-catecholamines, such as 5-S-cysteinyl-dopamine, 5-S-glutathionyl-dopamine and derived benzothiazines, are endogenous metabolites formed in the dopamine oxidative degradation pathway. Those metabolites have been shown to be highly toxic to neurons in the substantia nigra pars compacta, activating molecular mechanisms that ultimately lead to neuronal death. In this review we describe the origin, formation and the toxic effects of 5-S-cysteinyl-dopamine and its oxidative derivatives that cause death to dopaminergic neurons. Furthermore, we correlate the formation of those metabolites with the neurodegeneration progress in PD. In addition, we present the reported neuroprotective strategies of products that protect against the cellular damage of those thio-catecholamines. Finally, we discuss the advantages in the use of 5-S-cysteinyl-dopamine as a potential biomarker for PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease with the highest incidence worldwide in adults over 85 years old (Pringsheim et al., 2014; Hirsch et al., 2016). PD is characterized by motor and non-motor symptoms. Motor symptoms include postural instability, muscular rigidity, bradykinesia and resting tremor, while non-motor symptoms are characterized by cognitive and autonomic alterations (Titova et al., 2017; Schapira et al., 2017).

The pathology of PD is characterized by specific death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Neural loss is most likely due to the induced damage of the Lewy bodies, which are formed from the insoluble nucleation of misfolded alpha-synuclein (a-syn) protein in addition to the mitochondrial dysfunction (Goedert et al., 2013; Villar-Pique et al., 2016; Chen et al., 2019). The mitochondrial alteration is characterized by ATP depletion. This disrupts the storage of dopamine in vesicles, contributing to cytoplasmic formation of oxidized dopamine metabolites (Bisaglia et al., 2007; Bhattacharjee and Borah, 2016; Lotharius and Brundin, 2002a,b; Stokes et al., 1999). Oxidized dopamine products, such as dopamine quinones (DA-Q), mediate neuromelanin formation. However, they can also induce dopaminergic neuronal damage, which initiates key molecular mechanisms in PD. Recent studies conducted with dopaminergic neurons from PD patients demonstrated that mitochondrial oxidative stress leads to dopamine oxidized accumulation (Burbulla et al., 2017; Mor et al., 2017). As seen in these studies, oxidized dopamine initiates a time-dependent cascade, inducing glucocerebrosidase enzymatic depletion, lysosomal dysfunction and increased misfolding aggregation of a-syn. These findings support that dopamine oxidation is a key factor that increases neural damage in the SNpc.

The oxidative metabolism of dopamine leads to the formation of dopamine quinone metabolites, such as the 3,4-dopamine-o-quinone, aminochrome and 5,6-indolequinone. Extensive research of these metabolites in cellular and animal models has revealed a specific neurotoxicity to dopaminergic neurons (Hastings et al., 1996; Goldstein et al., 2014; Bisaglia et al., 2007; 2010; Muñoz et al., 2012; Monzani et al., 2019). However, not all the oxidation of dopamine leads to the formation of the aforementioned dopamine quinone metabolites; the thio-

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catecholamines, which are characterized by a sulfur atom in their molecular structure, are also formed through the dopamine oxidative degradation pathway. Common thio-catecholamines include the 5-S-glutathionyl-dopamine (5-S-GSH-DA) and 5-S-cysteinyl-dopamine (5-S-Cys-DA) conjugates (Tse et al., 1976; Graham, 1978; Ito and Fujita, 1982). Several studies have confirmed the neurotoxicity of 5-S-Cys-DA along with its benzothiazines. However, the susceptibility and progression of neural dysfunction that is induced by those thio-catecholamines in PD are not well understood. In this review, we first present the endogenous route formation of 5-S-GSH-DA and 5-S-Cys-DA with its benzothiazines. Then we describe their neurotoxic damage related to the activation of characteristic molecular mechanisms found in PD. In addition, we present the reported neuroprotective strategies against the 5-S-Cys-DA toxicity. Finally, we discuss the advantage of using 5-S-Cys-DA as a potential biomarker in the diagnosis of Parkinson's disease.

2. Oxidative metabolism of dopamine: dopamine quinone and thio-catecholamine formation

Dopamine (DA) is synthesized in the dopaminergic neuron by the enzymatic action of tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase (AADC). The amino acid tyrosine is hydroxylated by TH to form L-DOPA, which is further decarboxylated by AADC in the final formation of dopamine. (See Fig. 1. Reaction 1) (Meiser et al., 2013; Daubner et al., 2011). Immediately after the synthesis, the vesicular monoamine transporter 2 (VMAT-2) internalizes DA inside the vesicle through an active transport mechanism (Vergo et al., 2007). The vesicle, which has an internal acidic pH, stabilizes and stores DA; then DA is transported and released into the synapse. After the release, dopamine transporters (DAT) in the nigrostriatal terminal, reuptake DA from the synaptic cleft into the neuron. Nevertheless, perturbations in both the storage and reuptake of DA, such as the presence of pesticides and misfolded proteins, facilitates its cytoplasmic accumulation and further degradation (Mulvihill, 2019; Lotharius and Brundin, 2002a,b; Chedik et al., 2017). Free cytoplasmic DA is rapidly degraded through the enzymatic or oxidative pathway.

2.1. Enzymatic degradation of DA

DA degradation can take place in the dopaminergic neuron or in the surrounded glial cells, depending on where DA uptake occurs after the release. DA degradation inside the neuron is mediated by the enzymes monoamine oxidase (MAO) and aldehyde dehydrogenase (ALDH). MAO catalyzes the formation of DA into the intermediate product 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is further oxidized by ALDH to form 3,4-dihydroxyphenilacetic acid (DOPAC). Alternatively, DA degradation by glial cells leads to the formation of homovanillic acid (HVA) by two pathways: 1) MAO and ALDH convert DA into DOPAC, following the aforementioned enzymatic pathway, then DOPAC is converted into HVA by the enzyme catechol-o-methyltransferase (COMT); and 2) DA is metabolized into 3-methoxytyramide (3-MT) and 3-methoxy-4-hydroxyphenylacetaldehyde (MHPA) by COMT and MAO, respectively; then ALDH converts MHPA into HVA. DOPAC and HVA are the main final metabolites in the DA enzymatic degradation (Eisenhofer et al., 2004; Yu et al., 2016; Myöhänen et al., 2010). (See Fig. 1. Reactions 2 and 3).

2.2. Oxidative degradation of DA

The oxidative DA pathway starts with the pH change from the synaptic vesicle (pH 5.4) to the cytoplasm (pH 7.4) and in the presence of molecular oxygen conditions, leading to the spontaneous oxidation of dopamine (Herlinger et al., 1995; Linert et al., 1996). Moreover, DA oxidation is catalyzed by the presence of metallic ions such as iron (III),

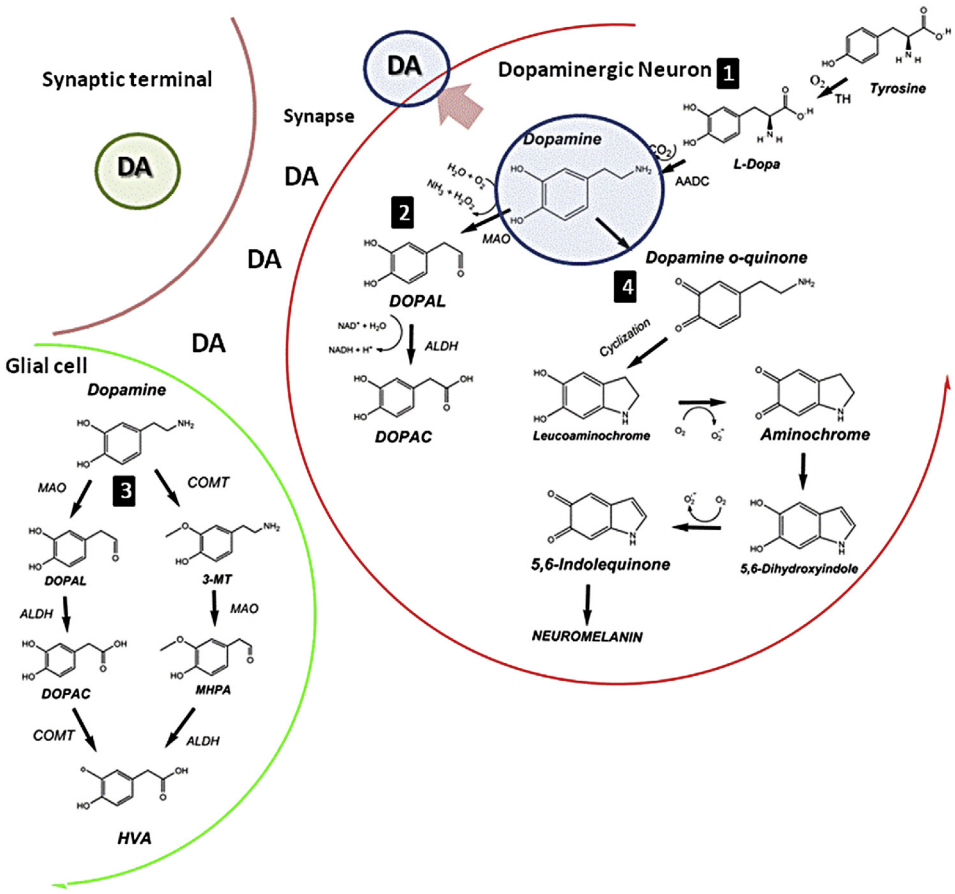

Fig. 1. Synthesis and metabolism of dopamine. Reaction 1. Enzymatic synthesis of DA, vesicular storage and release into the synapse. Reaction 2. Enzymatic degradation of DA inside the neuron to form DOPAL and finally DOPAC. Reaction 3. Enzymatic degradation of DA in glial cell to form HVA. Reaction 4. Oxidative degradation of DA through the formation of dopamine o-quinone, aminochrome, 5,6-indolequinone and neuromelanin. (Abbreviations: Aromatic amino acid decarboxylase (AADC); aldehyde dehydrogenase (ALDH); catechol-o-methyltransferase (COMT); monoamine oxidase (MAO); 3,4-dihydroxyphenylacetaldehyde (DOPAL); 3,4-dihydroxyphenilacetic acid (DOPAC); homovanillic acid (HVA); 3-methoxytyramide (3-MT); 3-methoxy-4-hydroxyphenylacetaldehyde (MHPA) and tyrosine hydroxylase (TH)).

copper (II) and manganese (III), as well as by the action of enzymes, such as xanthine oxidase (XO), cytochrome P450 (CYP450), prostaglandin H synthase (PGHS) and lactoperoxidase (LPO) (Sun et al., 2018; Pham and Waite, 2014; Sulzer and Zecca, 2000; Muñoz et al., 2012). The first step in the DA oxidation pathway leads to the formation of the intermediate 3,4-dopamine-o-quinone, which is prone to intramolecular cyclization in the formation of aminochrome. The aminochrome product can be further oxidized to form 5,6-indolequinone (See Fig. 1. Reaction 4). Under physiological conditions, the aforementioned metabolites take part in the formation of neuromelanin, which is the final product in the DA oxidative pathway. The metabolites aminochrome and 5,6-indolequinone have been studied extensively in several *in vitro* and *in vivo* models, demonstrating their severe toxicity to dopaminergic neurons. This toxicity is thought to be the cause of many parkinsonian symptoms, as discussed by several researchers (Asanuma et al., 2004; Solano et al., 1999; Sulzer and Zecca, 2000; Yoshimoto et al., 2005; Goldstein et al., 2014). Such evidences indicate that the excessive production of dopamine quinones is related to the disruption of neuromelanin formation, and is partly responsible for the increase in the concentration of oxidized DA metabolites (Monzani et al., 2019).

2.3. Formation of 5-S-glutathionyl-dopamine and 5-S-cysteinyl-dopamine

The dopamine-o-quinone (DA-o-Q), the first product in the oxidative pathway of DA, is an electron deficient intermediate. It easily reacts with rich electron molecules, such as those containing a sulfur atom. The amino acid l-cysteine (l-cys) and the reduced glutathione (GSH) tripeptide are sulfur-containing molecules of high concentration in the brain (Zeevalk et al., 2008; Dringen, 2000). In the presence of l-cys, the aromatic ring of DA-o-Q reacts covalently with the sulfhydryl group of l-cys, resulting in the formation of three isomers: 2-S-cysteinyl-dopamine (2-S-Cys-DA), 5-S-cysteinyl-dopamine (5-S-Cys-DA) and 2,5-S-cysteinyl-dopamine (2,5-S-Cys-DA), where 5-S-Cys-DA is the most abundant (Jameson et al., 2004; Zhang and Dryhurst,1994). The reaction between DA-o-Q and GSH leads to the formation of the 5-S-glutathionyl-dopamine (5-S-GSH-DA) conjugate, as the main product (Bisaglia et al., 2010) (See Fig. 2. Reaction 1). However, experimental studies have shown that 5-S-GSH-DA is rapidly catabolized by the enzymes gamma-glutamyl transferase (GGT) and dipeptidases, resulting in the formation of 5-S-Cys-DA (Allen et al., 2013; Dickinson and Forman, 2002). Furthermore, several studies have reported the increased activity of GGT in brain samples of PD patients, which might support its critical role in the conversion of 5-S-GSH-DA into 5-S-Cys-DA (Dagnino-Subiabre et al., 2000; Shen et al., 1996; Sagara et al., 1993).

2.4. Formation of benzothiazines of 5-S-cysteinyl-dopamine

The 5-S-Cys-DA conjugate is a molecule that is prone to fast oxidation into secondary products when exposed to superoxide anion ($O_2^{\cdot-}$), metallic ions, and other oxidants. The oxidative pathway of 5-S-Cys-DA leads to the formation of an intermediate quinone of 5-S-cysteinyl-dopamine o-quinone (5-S-Cys-DA-o-Q), which is quickly converted into the bicyclic o-quinone imine through a condensation reaction. The aforementioned product is then reduced by a second molecule of 5-S-Cys-DA, resulting in the formation of the benzothiazine 7-(2-aminoethyl)-3,4-dihydro-5-hydroxy-2H-1,4-benzothiazine-3-carboxylicacid (DHBT-1). (Shen et al., 1997; Zhang and Dryhurst, 1995a; Shen and Dryhurst,1996). (See Fig. 2, Reaction 2). Nevertheless, *in vitro* studies have shown that DHBT-1 is able to enter into further oxidative pathways, leading to the formation of oxidized benzothiazines, such as the 7-(2-aminoethyl)-5-hydroxy-1,4-benzothiazine-3-carboxylic acid (BT-1) and 7-(2-aminoethyl)-5-hydroxy-1,4-benzothiazine (BT-2). However, both BT-1 and BT-2 are prone to further oxidization under a high oxidative environment to form derivative products (Shen et al., 1997; Zhang and Dryhurst, 1995b). (See Fig. 2, Reaction 3).

More recently, an alternative reaction of 5-S-Cys-DA with hypochlorite (OCl^-) was described. Hypochlorite, which is formed in the reaction of chlorine (Cl_2^-) with hydrogen peroxide (H_2O_2) and catalyzed by myeloperoxidases, reacts with 5-S-Cys-DA to form the conjugate hypochlorite-oxidized cysteinyl-dopamine (HOCD). The *in vitro* formation of HOCD increases the concentration of reactive oxygen species, yielding oxidative stress and severe toxic damage to dopaminergic neurons (Mehta et al., 2016) (See Fig. 2. Reaction 4).

In the dopaminergic neuron, where the equilibrium redox is preserved, the 5-S-Cys-DA conjugate is normally formed at a very low concentration, which is also structurally part of neuromelanin (Sulzer et al., 2000). However, quantitative analysis of brain tissues of rich dopaminergic regions and in cerebrospinal fluid (CSF) of patients diagnosed with PD demonstrated significantly increased levels of 5-S-Cys-DA (Fornstedt and Carlsson, 1990; Fornstedt et al., 1990b). This finding supports the role of the diverged DA oxidative pathway in the endogenous formation of 5-S-Cys-DA. A possible explanation of the increased formation of 5-S-Cys-DA might be the disruption in the DA reuptake mechanism, which blocks the storage of the synaptic vesicle and leads to cytosolic accumulation of DA and its further oxidation (Mulvihill, 2019; Monzani et al., 2019; Caudle et al., 2007).

On the other hand, reduced glutathione (GSH), the most abundant antioxidant in brain cells, is found in physiological concentration at approximately 1–4 mM (Rae and Williams, 2017; Aoyama and Nakaki, 2013). However, extensive studies have found a marked reduction in the levels of both GSH and l-cysteine in patients with PD, which are likely to appear in the early stages of the disease and as it progresses (Rae and Williams, 2017; Smeyne and Smeyne, 2013; Müller and Muhlack, 2012; Sian et al., 1994). In addition, several studies have reported a similar *in vivo* discrepancy in the levels of reduced glutathione (GSH) against oxidized glutathione (GSSG). Nevertheless, in postmortem analysis of PD samples the GSH levels were considerable decreased, but not GSSG (Canals et al., 2001; Ibi et al., 1999; Jurma et al., 1997). Furthermore, in these studies the unbalanced GSH/GSSG ratio was accompanied by the increased activity of gamma-glutamyl transferase (GGT), the key enzyme to convert 5-S-GSH-DA into 5-S-Cys-DA (Chinta et al., 2006; Dauer and Przedborski, 2003; Sian et al., 1994). All of these findings indicate that the reduced intracellular levels of GSH and l-cys, are linked to the increased formation of conjugates with the dopamine-o-quinone intermediate in the oxidative DA pathway. Furthermore, the enhanced formation of the thio-catecholamines might be due to the presence of elevated cell oxidative stress (Graham et al., 1978). Moreover, the formation of 5-S-Cys-DA or 5-S-GSH-DA occurs at a very rapid constant rate (200/s) in comparison to the cyclic product formation of aminochrome and 5,6-indolequinone (formed at a slow constant rate of 0.15/s) (Tse et al., 1976; Bisaglia et al., 2010). Such evidence might indicate that in the pathophysiological course of PD, the thio-catecholamines 5-S-GSH-DA, 5-S-Cys-DA and DHBT-1 appear at the initial stages of the disease, while the cyclic dopamine quinones, aminochrome and 5,6-indolequinone, might be formed in mid- or advanced-stages.

3. The 5-S-Cys-DA conjugate and its derivative benzothiazines: implications for PD

Several studies have shown through *in vitro* and *in vivo* experiments that 5-S-Cys-DA and oxidized benzothiazines cause severe damage to dopaminergic neurons. The cellular damage caused by those thio-catecholamines is comparable to the neurotoxic effect produced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) (Langston, 2017; Lotharius and O'Malley, 2000; Hernandez-Baltazar et al., 2017). Several groups have described the participation of 5-S-Cys-DA and DHBT-1 in some characteristic PD molecular mechanisms, such as the following:

i) ***Mitochondrial dysfunction and oxidative stress***. It is well known

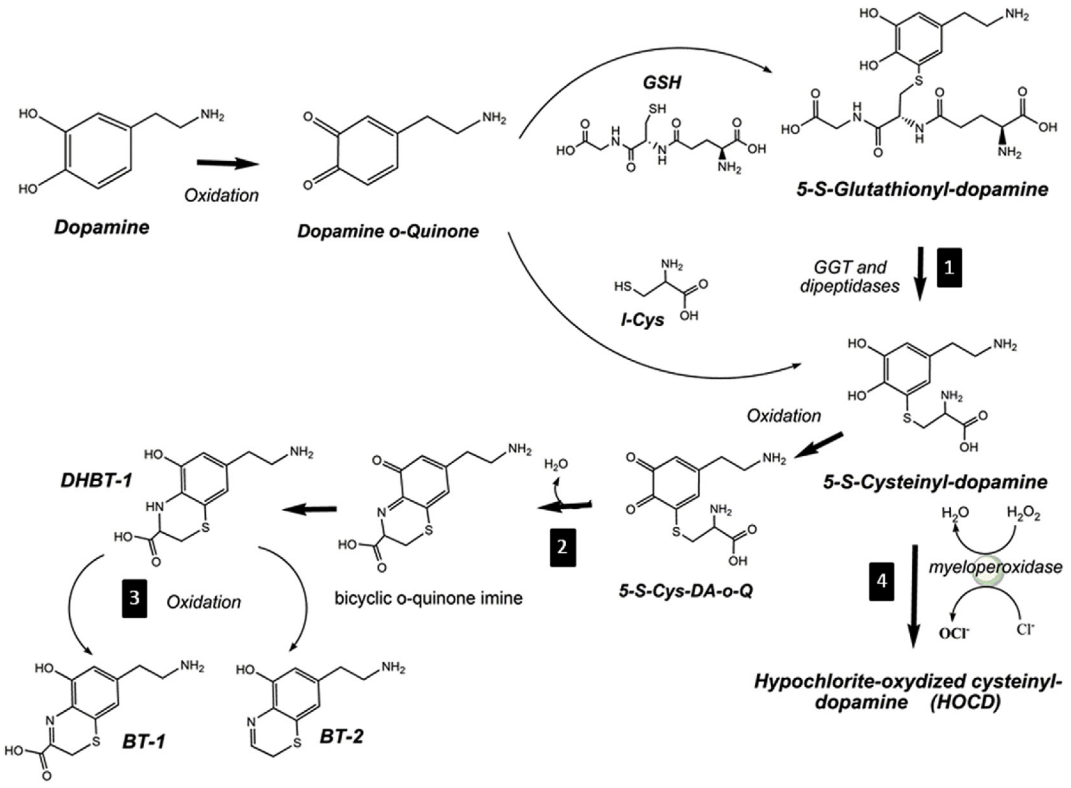

Fig. 2. Synthesis of thio-catecholamines and dihydrobenzothiazines. Reaction 1. Formation of 5-S-glutathionyl-dopamine (5-S-GSH-DA) and its enzymatic degradation to form 5-S-Cysteinyl-dopamine (5-S-Cys-DA). Reaction 2. Oxidation of 5-S-Cys-DA to form benzothiazine 7-(2-aminoethyl)-3,4-dihydro-5-hydroxy-2H-1,4-benzothiazine-3-carboxylic acid (DHBT-1). Reaction 3. formation of 7-(2-aminoethyl)-5-hydroxy-1,4-benzothiazine-3-carboxylic acid (BT-1) and 7-(2-aminoethyl)-5-hydroxy-1,4-benzothiazine (BT-2). Reaction 4. Formation of hypochlorite-oxidized cysteinyl-dopamine (HOCD). (Abbreviations: glutathione (GSH); hypochlorite (OCl^-); 5-S-Cysteinyl-dopamine-o-quinone (5-S-Cys-DA-o-Q) and gamma-glutamyl transferase (GGT)).

that oxidative stress and mitochondrial dysfunction are key factors of cellular damage in the physiology of PD (Nguyen et al., 2019; Subramaniam and Chesselet, 2013; Santiago-López et al., 2010). The role of 5-S-Cys-DA in neural damage through the mitochondrial dysfunction and enhanced oxidative stress has been well established. As *Mosca* and colleagues demonstrated by injecting in mice and in cellular incubation, 5-S-Cys-DA initiates the activation of a cascade of events when concentrated at the micromolar range. The mitochondrial activity is severely affected at the beginning of the exposure (Mosca et al., 2006). 5-S-Cys-DA is easily internalized within the cell, disturbing its homeostasis and causing: 1) Increased levels of reactive oxygen species, which induces protein carbonylation and lipid oxidation; 2) alteration of cytoplasmic calcium homeostasis, leading to depolarization and a decrease of the mitochondrial membrane potential; 3) reduction in the efficiency of the mitochondrial electron transport chain and; 4) a considerable reduction in the intracellular concentration of antioxidants superoxide dismutase (SOD) and GSH (Vauzour et al., 2014; Aureli et al., 2014). In addition, reported experiments have shown that 5-S-Cys-DA is able to suppress the mitochondrial activity through the inhibition of the respiratory complex I, leading to activate programmed cellular death mechanisms, such as the cytochrome *c* release and activation of caspases 3, 8 and 9. (Mosca et al., 2008, 2006; Spencer et al., 2002).

More recently, *Vauzour* and colleagues described the mechanism that takes part in the intracellular oxidation of 5-S-Cys-DA into DHBT-1, showing extensive cell damage in a dose time dependent pathological cascade (Vauzour et al., 2014). Under the first exposition time, 5-S-Cys-DA is internalized and intracellularly oxidized, leading to the activation of the extracellular-signal-regulated kinase 2 (ERK2) and the caspase 8, key events in the initiation of programmed cellular death. Further oxidation of 5-S-Cys-DA activates secondary apoptotic mechanisms, such as the apoptosis signal-regulating kinase 1 (ASK1), the phosphorylation of c-Jun N-terminal kinase (JNK) and c-Jun (Ser73), p38 and the caspases 3, 7 and 9. Nevertheless, the severe mitochondrial inhibition occurs after long exposition time; the conversion of 5-S-Cys-DA into DHBT-1 requires over 3 h to be completed. In support of the toxic role of DHBT-1 to mitochondria, *Li and Dryhurst* studied the toxic effect of DHBT-1 in cultured intact rat mitochondria (Li and Dryhurst, 2001). DHBT-1 toxicity starts with an easy diffusion into the mitochondrial membrane, leading to fast irreversible inhibition of the respiratory complex I with severe concomitant damage to mitochondrial complex IV, alpha-ketoglutarate dehydrogenase complex (KGDHC) and pyruvate dehydrogenase complex (PDHC) (Xin et al., 2000). In an elevated reactive oxygen species environment, DHBT-**1** is prone to fast oxidation to form the dihydrobenzothiazines BT-1 and BT-2 (Li et al., 1998). Similar experiments show that BT-1 and BT-2 cause enhanced mitochondrial damage, in comparison to DHBT-1 (Li and Dryhurst, 1997).

ii) **Alpha-synuclein aggregation and stress of endoplasmic reticulum.** *In vivo* and *in vitro* experiments have shown the upregulation of a-syn immediately after the exposition to 5-S-Cys-DA. The a-syn upregulation was accompanied by the depletion in the expression of the protein ERp57, a key lumenal protein that is responsive to endoplasmic reticulum (ER) stress. This induces the unfolded protein response (UPR) (Aureli et al., 2014). In addition, 5-S-Cys-DA plays an important role in the fibril formation of a-syn by increasing its aggregation and cytoplasmic accumulation. This event is modulated in a time dependent process, but it is intensified under exacerbated intracellular oxidative stress (Zafar et al., 2006).

Several experiments support the notion that elevated oxidative stress in dopaminergic neurons may contribute to a-syn aggregation and vice versa, creating a vicious cycle and leading to increase the PD neurodegeneration (Mor et al., 2017; Wong and Krainc, 2017; Conway et al., 2001). Although the toxic damage of 5-S-Cys-DA has been described, it is unclear whether 5-S-Cys-DA or secondary dopamine oxidized derivatives are responsible for a-syn misfolding and aggregation.

Sidell and colleagues have shown that 5-S-Cys-DA interferes in the synaptic terminal DA reuptake of dopamine transporters, which increases the formation of dopamine quinone subproducts. This observation indicates that the vesicular traffic interference causes deleterious neurological activity (Sidell et al., 2001). Nevertheless, the inhibition mechanism of the DA vesicular reuptake by oxidized dopamine remains elusive. A possible explanation is the contribution of thiocatecholamines in the inhibition of dopamine transporters and through the formation of enzymatic adducts with VMAT-2. This could potentially drive DA oxidation into a vicious circle that results in the formation of endogenous thio-catecholamines induced by rapid DA oxidation (Caudle et al., 2007; Whitehead et al., 2001).

Related experiments have produced varying results. Some have demonstrated the impact of 5-S-Cys-DA on DNA, which induces oxidation to the purine and pyrimidine bases and causing oligonucleosomal DNA fragmentation (Mosca et al., 2006). These DNA abnormalities might lead to epigenetic changes, such as DNA methylation or histone modifications (Henderson-Smith et al., 2019; Cobos et al., 2018). A large body of evidence suggests that epigenetic modifications have a relevant impact on the etiology and progression of PD (van Heesbeen and Smidt, 2019; Navarro-Sánchez et al., 2018; Jakubowski and Labrie, 2017). A summary of the impacts of 5-S-Cys-DA and the dihydrobenzothiazines to dopaminergic neurons is graphically described in Fig. 3.

4. Inhibition of the neurotoxic effects of 5-S-Cys-DA

Growing evidence has demonstrated the neuroprotective capacity of several compounds to slow down the cellular damage of oxidized dopamine metabolites. Some of the common products used for this aim are the N-acetylcysteine (NAC), GSH, ascorbic acid, taurine, dithiothreitol, vitamin C, vitamin E and the Coenzyme Q10 (Carrera et al., 2018; Kita et al., 2014; Filograna et al., 2016; Figueroa-Méndez and Rivas-Arancibia, 2015). In addition, some polyphenolic compounds have been shown to provide effective neuroprotection to dopaminergic neurons by attenuating the mitochondrial dysfunction, reducing both the levels of oxidative stress and inflammatory responses, and inhibiting the fibril accumulation of a-syn (Kujawska and Jodynis-Liebert, 2018; Jung and Kim, 2018; Magalingam et al., 2015).

Additional studies have shown that some natural polyphenols, both flavonoids and non-flavonoids, are able to prevent the formation of 5-S-Cys-DA and reduce its cell toxicity (Goldstein et al., 2016a,b; Cooper et al., 2008; Vauzour et al., 2007, 2010). Experiments in cultured cells have shown that (+)-catechin and caffeic acid avoid the formation of thio-catecholamines. The *in vitro* incubation of those polyphenols with tyrosinase and dopamine, and in the presence of l-cysteine, leads to oxidized polyphenols while blocking the oxidation of dopamine and forming non-toxic adducts of cysteinyl-polyphenols. Furthermore, the hesperetin, a flavanone, prevents the 5-S-Cys-DA formation by blocking the enzymatic action of tyrosinase, inhibiting the polyphenol adduct formation (Vauzour et al., 2007). In addition, a rich variety of polyphenolic compounds have also shown *in vitro* neuroprotective capacity. This includes compounds such as pelargonidin, quercetin, hesperetin, caffeic acid, p-Coumaric acid, hydroxyphenethyl alcohol, tyrosol, epicatechin and the 3′-o-methyl-(−)-epicatechin. The pre-treatment of cortical neurons with those aforementioned polyphenols significantly reduces the toxic damage of 5-S-Cys-DA after its exposure (Vauzour et al., 2008, 2010). More recently, *Goldstein* and colleagues demonstrated the double *in vitro* neuroprotective effect of the 3,4-dihydroxyphenylethanol (DOPET), a phenolic compound found in olive oil and red wine. This compound reduces the toxicity of 5-S-Cys-DA (Goldstein et al., 2017, 2016) and DOPAL, which is a toxic intermediate metabolite in the metabolic dopamine pathway, and has also been linked to dopaminergic neuron death (Goldstein et al., 2014; Casida et al., 2014; Marchitti et al., 2007). The aforementioned evidence highlights the neuroprotection of natural polyphenols against the toxic endogenous formation of oxidized dopamine metabolites. These strategies shed light onto the neuroprotective capacity of such products, which may help advance the future development of clinical therapies in the treatment of patients with PD.

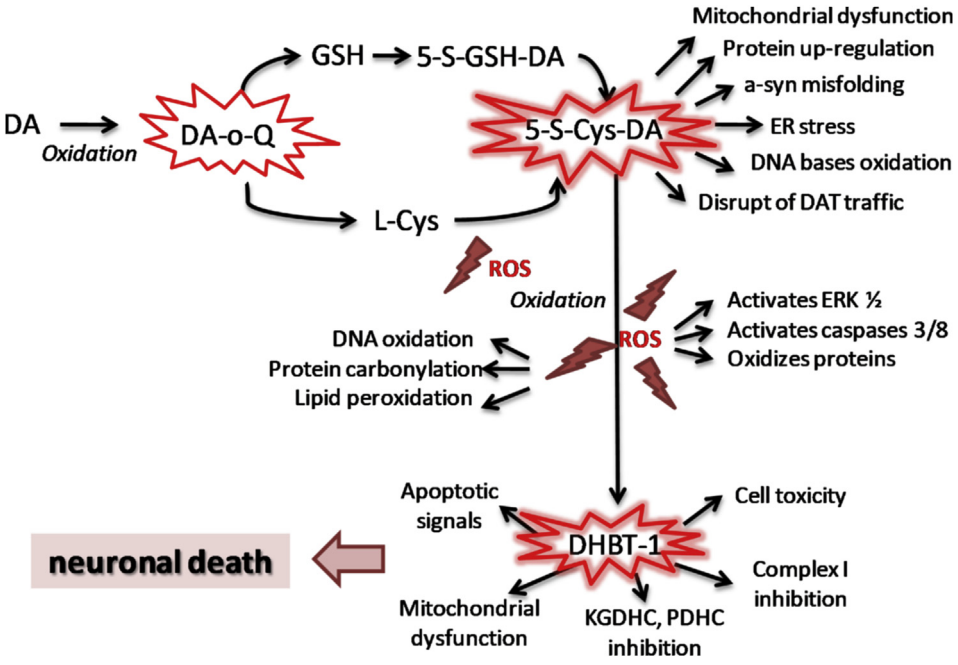

Fig. 3. Toxic effects of dopamine oxidation through the endogenous formation of dopamine-o-quinone, 5-S-cysteinyl-dopamine (5-S-Cys-DA) and 7-(2-aminoethyl)-3,4-dihydro-5-hydroxy-2H-1,4-benzothiazine-3-carboxylic acid (DHBT-1). Formation of 5-S-Cys-DA induces cell toxicity. The oxidation of 5-S-Cys-DA to form DHBT-1 enhances damage. These metabolites cause damage to dopaminergic neurons by inducing mitochondrial dysfunction, an increase in oxidative stress, protein and DNA damage, endoplasmic reticulum (ER) stress, and the activation of key apoptotic signals; this leads to neural death, which may contribute to the pathogenesis and progress of Parkinson's disease. (Abbreviations: reactive oxygen species (ROS); reduced glutathione (GHS); 5-S-glutahionyl-dopamine (5-S-GSH-DA); extracellular signal regulated kinase 1/2 (ERK 1/2); dopamine o-quinone (DA-o-Q); dopamine transporter (DAT); alpha-ketoglutarate dehydrogenase complex (KGDHC); pyruvate dehydrogenase complex (PDHC); alpha-synuclein (a-syn)).

5. 5-S-Cys-DA as biomarker for PD diagnosis

Motor symptoms in PD are evident after the loss of 70% of dopaminergic neurons in the SNpc (Hirsch et al., 2016). This drawback reveals the urgent necessity to develop strategies for the detection of PD at early stages. Metabolites formed at the beginning of the disease, such as derivative dopamine products, could be used as biomarkers for the early diagnosis of PD. This could potentially provide an important means of differentiating PD from other pathologies that manifest in related parkinsonian syndromes (Parnetti et al., 2019; Yaping and Weidong, 2019).

Currently, there are several prospective biomarkers of high sensitivity and diagnostic potential for PD (Khodadadian et al., 2018; Maass et al., 2018; Delenclos et al., 2016). Six biomarker groups for PD diagnosis have been described: i) neurotransmitters, neuromodulators and related substances; ii) endogenous neurotoxins; iii) oxidative stress markers; iv) inflammatory and immunologic markers; v) growth and neurotrophic factors; and vi) protein biomolecules related to PD (Jiménez-Jiménez et al., 2014). Nevertheless, none of the thio-catecholamines previously described, have been included in these categories. Detection of metabolites coming from the endogenous metabolism of DA may provide an effective means towards identifying biomarkers for PD diagnosis.

*Rosengre*n and colleagues first detected 5-S-Cys-DA in humans and other mammals (Rosengren et al., 1985; Fornstedt et al., 1986, 1990a). Through autopsies of the human brain they detected 5-S-Cys-DA and other thio-catecholamines in regions rich in dopamine. High levels of 5-S-Cys-DA were identified only in the caudate nucleus, putamen, globus pallidus and substantia nigra (SN); where the SN showed the highest concentration (Fornstedt and Carlsson, 1989). Notably, the quantification of 5-S-Cys-DA was considerably high in samples presenting high depigmentation in the SN (Fornstedt et al., 1990a). Furthermore, when comparing results between PD and non-PD patients, they found that the level of the ratio of 5-S-Cys-DA to DA was ten times higher in patients diagnosed with PD (Fornstedt and Carlsson, 1991; Fornstedt et al., 1990a). Increased levels of circulating 5-S-Cys-DA were also detected in cerebrospinal fluid (CSF) of patients with PD (Carlsson and Fornstedt, 1991a; Fornstedt et al., 1990a). In that sense, *Carlsson and Fornstedt* suggested that measuring the 5-S-Cys-DA to DA ratio can be used as biomarker for the diagnosis of PD (Carlsson and Fornstedt, 1991b). However, the circulating levels of DA in the 5-S-Cys-DA/DA ratio hardly reflect the neurodegeneration state of the dopaminergic neuron in the SNpc. In addition, DA has rarely been considered to be a specific PD metabolite and its use as biomarker is contested. (Ishibashi et al., 2010; Sossi et al., 2002). On the other hand, clinical measurements in CSF samples of PD patients revealed a decreased total concentration of HVA, while the levels of the 5-S-Cys-DA to HVA ratio were considerably increased. This led researchers to hypothesize that the quantification of the 5-S-Cys-DA/HVA ratio could represent a better biomarker for PD (Cheng et al., 1996). However, the measurement of those metabolites was performed in patients diagnosed with PD several years after the study was first conducted. In addition, the patients were being treated with levodopa (L-DOPA). Actual levels of DA metabolites must be carefully examined. For example, in cases of levodopa treatment, L-DOPA can induce adverse effects, such as the levodopa-induced dyskinesia (LID). (Romagnolo et al., 2018; Rajabally and Martey, 2013). On the other hand, only measuring HVA in CSF can be misleading because it is not specific to the disease. As previously described, glial cells synthesize HVA; thus, the measurement of HVA hardly represents the real state of DA metabolism in the dopaminergic neuron (Lloyd et al., 1975).

Clinical trials by *Goldstein* and colleagues, which include analytic and neuroimaging studies, corroborate the use of 5-S-Cys-DA as a biomarker in the diagnosis of PD. This was demonstrated by measuring the levels of 5-S-Cys-DA and DOPAC in patients diagnosed with three different parkinsonian syndromes: PD, parkinsonian multiple system atrophy (MSA-P) and pure autonomic failure (PAF). Quantitative detection of the ratio of 5-S-Cys-DA to DOPAC was more than doubled in patients with PD and MSA-P, while no significant changes were observed in patients with PAF (Goldstein et al., 2016a,b, 2012). These findings support the use of DOPAC and the ratio of 5-S-Cys-DA/DOPAC as biomarkers for PD diagnosis. Furthermore, DOPAC is a metabolite with a much higher specificity to the index of neural damage in the SNpc, while the 5-S-Cys-DA/DOPAC ratio indicates both the cytoplasmic oxidative state of DA and the endogenous thio-catecholamine formation in the progress of the disease. The findings from this research, as well as the identification of circulating antibodies against cysteinyl-catecholamines in PD patients, indicate the specificity of thio-catecholamines to PD (Salauze et al., 2005). Therefore, in the recent search for specific PD biomarkers, the combination of DA derived products, such as oxidized dopamine, 5-S-Cys-DA, DOPAC, aminochrome and 5,6-indolequinone, could be used for accurate diagnosis of PD.

6. Conclusions

Parkinson's disease is a multifactorial pathology, and its origin is still poorly understood. A common pathognomonic characteristic of this disease is the altered metabolism of dopamine in the dopaminergic neurons of the substantia nigra pars compacta. There is substantial evidence of the altered metabolism of DA in PD, which occurs through its enzymatic and oxidative pathways and results in the formation of endogenous toxic metabolites. These metabolites are responsible for cellular damage and death, as well as for activating several key molecular mechanisms in the pathology of PD. The 5-S-Cys-DA metabolite and its benzothiazine (DHBT-1) are thio-catecholamines of endogenous formation that induce severe damage to dopaminergic neurons. Neural damage by 5-S-Cys-DA and DHBT-1 is characterized by mitochondrial dysfunction and ATP depletion, increased oxidative stress, protein carbonylation and DNA damage, as well as the activation of apoptotic signals. Neuroprotective products, such as polyphenols, reduce cell toxicity of oxidized dopamine and thio-catecholamines, which could help to develop further therapies for PD patients. The hindrance in the prognosis of PD in an early stage and the difficulty to differentiate it from other parkinsonian syndromes has incentivized researchers to investigate the role of metabolites in PD prognosis. The 5-S-Cys-DA metabolite, present in brain tissues and biological fluids of PD patients, has shown a strong performance as a specific biomarker with the advantage of differentiating PD from other parkinsonian syndromes. Finally, future research in the study of combined metabolites from the enzymatic and oxidative pathway of DA, such as 5-S-Cys-DA, DOPAC, aminochrome and 5,6-indolequinone, might provide key information in the neurogenerative progress of PD.

Conflicts of interest

Declarations of interest conflicts: none.

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Appendix A. Supplementary data

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References

Allen, G.F., Ullah, Y., Hargreaves, I.P., Land, J.M., Heales, S.J., 2013. Dopamine but not l-dopa stimulates neural glutathione metabolism. Potential implications for Parkinson's and other dopamine deficiency states. Neurochem. Int. 62, 684–694.

Aoyama, K., Nakaki, T., 2013. Impaired glutathione synthesis in neurodegeneration. Int. J. Mol. Sci. 14, 21021–21044.

Asanuma, M., Miyazaki, I., Diaz-Corrales, F.J., Ogawa, N., 2004. Quinone formation as dopaminergic neuron-specific oxidative stress in pathogenesis of sporadic Parkinson's disease and neurotoxin-induced. Acta Med. Okayama 58, 221–233.

Aureli, C., Cassano, T., Masci, A., Francioso, A., Martire, S., Cocciolo, A., Chichiarelli, S., Romano, A., Gaetani, S., Mancini, P., Fontana, M., d'Erme, M., Mosca, L., 2014. 5-S-cysteinyldopamine neurotoxicity: influence on the expression of α-synuclein and ERp57 in cellular and animal models of Parkinson's disease. J. Neurosci. Res. 92, 347–358.

Bhattacharjee, N., Borah, A., 2016. Oxidative stress and mitochondrial dysfunction are the underlying events of dopaminergic neurodegeneration in homocysteine rat model of Parkinson's disease. Neurochem. Int. 10, 48–55.

Bisaglia, M., Soriano, M.E., Arduini, I., Mammi, S., Bubacco, L., 2010. Molecular characterization of dopamine-derived quinones reactivity toward NADH and glutathione: implications for mitochondrial dysfunction in Parkinson disease. Biochim. Biophys. Acta 1802, 699–706.

Bisaglia, M., Mammi, S., Bubacco, L., 2007. Kinetic and structural analysis of the early oxidation products of dopamine: analysis of the interactions with alpha- synuclein. J. Biol. Chem. 282, 15597–15605.

Burbulla, L.F., Song, P., Mazzulli, J.R., Zampese, E., Wong, Y.C., Jeon, S., Santos, D.P., Blanz, J., Obermaier, C.D., Strojny, C., Savas, J.N., Kiskinis, E., Zhuang, X., Krüger, R., Surmeier, D.J., Krainc, D., 2017. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. Science 357, 1255–1261.

Canals, S., Casarejos, M.J., de Bernardo, S., Rodriguez-Martin, E., Mena, M.A., 2001. Glutathione depletion switches nitric oxide neurotrophic effects to cell death in midbrain cultures: implications for Parkinson's disease. J. Neurochem. 79, 1183–1195.

Carlsson, A., Fornstedt, B., 1991b. Catechol metabolites in the cerebrospinal fluid as possible markers in the early diagnosis of Parkinson's disease. Neurology 41, 50–51 discussion 52.

Carlsson, A., Fornstedt, B., 1991a. Possible mechanisms underlying the special vulnerability of dopaminergic neurons. Acta Neurol. Scand. Suppl. 136, 16–18.

Carrera, I., Fernandez-Novoa, L., Sampedro, C., Tarasov, V.V., Aliev, G., Cacabelos, R., 2018. Dopaminergic neuroprotection with atremorine in Parkinson's disease. Curr. Med. Chem. 25, 5372–5388.

Casida, J.E., Ford, B., Jinsmaa, Y., Sullivan, P., Cooney, A., Goldstein, D.S., 2014. Benomyl, aldehyde dehydrogenase, DOPAL, and the catecholaldehyde hypothesis for the pathogenesis of Parkinson's disease. Chem. Res. Toxicol. 27, 1359–1361.

Caudle, W.M., Richardson, J.R., Wang, M.Z., Taylor, T.N., Guillot, T.S., McCormack, A.L., Colebrooke, R.E., Di Monte, D.A., Emson, P.C., Miller, G.W., 2007. Reduced vesicular storage of dopamine causes progressive nigrostriatal neurodegeneration. J. Neurosci. 27, 8138–8148.

Chedik, L., Bruyere, A., Le Vee, M., Stieger, B., Denizot, C., Parmentier, Y., Potin, S., Fardel, O., 2017. Inhibition of human drug transporter activities by the pyrethroid pesticides allethrin and tetramethrin. PLoS One 12 e0169480.

Chen, C., Turnbull, D.M., Reeve, A.K., 2019. Mitochondrial dysfunction in Parkinson's disease-cause or consequence? Biology 8 pii: E38.

Cheng, F.C., Kuo, J.S., Chia, L.G., Dryhurst, G., 1996. Elevated 5-S- cysteinyldopamine/homovanillic acid ratio and reduced homovanillic acid in cerebrospinal fluid: possible markers for and potential insights into the pathoetiology of Parkinson's disease. J. Neural Transm. 103, 433–446.

Chinta, S.J., Kumar, J.M., Zhang, H., Forman, H.J., Andersen, J.K., 2006. Up regulation of gamma-glutamyl transpeptidase activity following glutathione depletion has a compensatory rather than inhibitory effect on mitochondrial complex I activity: implications for Parkinson's disease. Free Radic. Biol. Med. 40, 1557–1563.

Cobos, S.N., Bennett, S.A., Torrente, M.P., 2018. The impact of histone post-translational modifications in neurodegenerative diseases. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. S0925–4439, 30396–X.

Conway, K.A., Rochet, J.C., Bieganski, R.M., Lansbury Jr., P.T., 2001. Kinetic stabilization of the alpha-synuclein protofibril by a dopamine-alpha-synuclein adduct. Science 294, 1346–1349.

Cooper, A.J., Pinto, J.T., Krasnikov, B.F., Niatsetskaya, Z.V., Han, Q., Li, J., Vauzour, D., Spencer, J.P., 2008. Substrate specificity of human glutamine transaminase K as an aminotransferase and as a cysteine S-conjugate beta-lyase. Arch. Biochem. Biophys. 474, 72–81.

Dagnino-Subiabre, A., Cassels, B.K., Baez, S., Johansson, A.S., Mannervik, B., Segura-Aguilar, J., 2000. Glutathione transferase M2-2 catalyzes conjugation of dopamine and dopa o-quinones. Biochem. Biophys. Res. Commun. 274, 32–36.

Daubner, S.C., Le, T., Wang, S., 2011. Tyrosine hydroxylase and regulation of dopamine synthesis. Arch. Biochem. Biophys. 508, 1–12.

Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. Neuron 39, 889–909.

Delenclos, M., Jones, D.R., McLean, P.J., Uitti, R.J., 2016. Biomarkers in Parkinson's disease: advances and strategies. Park. Relat. Disord. 22 (Suppl. 1), S106–S110.

Dickinson, D.A., Forman, H.J., 2002. Cellular glutathione and thiols metabolism. Biochem. Pharmachol. 64, 1019–1026.

Dringen, R., 2000. Metabolism and functions of glutathione in brain. Prog. Neurobiol. 62, 649–671.

Eisenhofer, G., Kopin, I.J., Goldstein, D.S., 2004. Catecholamine metabolism: a contemporary view with implications for physiology and medicine. Pharmacol. Rev. 56, 331–349.

Figueroa-Méndez, R., Rivas-Arancibia, S., 2015. Vitamin C in Health and Disease: its role in the metabolism of cells and redox state in the brain. Front. Physiol. 6, 397.

Filograna, R., Beltramini, M., Bubacco, L., Bisaglia, M., 2016. Anti-oxidants in Parkinson's disease therapy: a critical point of view. Curr. Neuropharmacol. 14, 260–271.

Fornstedt, B., Bergh, I., Rosengren, E., Carlsson, A., 1990a. An improved HPLC-electrochemical detection method for measuring brain levels of 5-S-cysteinyldopamine, 5-S-cysteinyl-3,4-dihydroxyphenylalanine, and 5-S-cysteinyl-3,4-dihydroxyphenylacetic acid. J. Neurochem. 54, 578–586.

Fornstedt, B., Carlsson, A., 1989. A marked rise in 5-S-cysteinyl-dopamine levels in Guinea- pig striatum following reserpine treatment. J. Neural Transm. 76, 155–161.

Fornstedt, B., Pileblad, E., Carlsson, A., 1990b. In vivo autoxidation of dopamine in Guinea pig striatum increases with age. J. Neurochem. 55, 655–659.

Fornstedt, B., Rosengren, E., Carlsson, A., 1986. Occurrence and distribution of 5-S- cysteinyl derivatives of dopamine, DOPA and DOPAC in the brains of eight mammalian species. Neuropharmacology 25, 451–454.

Fornstedt, B., Carlsson, A., 1991. Effects of inhibition of monoamine oxidase on the levels of 5-S-cysteinyl adducts of catechols in dopaminergic regions of the brain of the Guinea pig. Neuropharmacology 30, 463–468.

Goedert, M., Spillantini, M.G., Del Tredici, K., Braak, H., 2013. 100 years of Lewy pathology. Nat. Rev. Neurol. 9, 13–24.

Goldstein, D.S., Holmes, C., Sharabi, Y., 2012. Cerebrospinal fluid biomarkers of central catecholamine deficiency in Parkinson 's disease and other synucleinopathies. Brain 135, 1900–1913.

Goldstein, D.S., Holmes, C., Sullivan, P., Jinsmaa, Y., Kopin, I.J., Sharabi, Y., 2016a. Elevated cerebrospinal fluid ratios of cysteinyl-dopamine/3,4-dihydroxyphenylacetic acid in parkinsonian synucleinopathies. Park. Relat. Disord. 31, 79–86.

Goldstein, D.S., Jinsmaa, Y., Sullivan, P., Holmes, C., Kopin, I.J., Sharabi, Y., 2016b. 3,4-Dihydroxyphenylethanol (Hydroxytyrosol) mitigates the increase in spontaneous oxidation of dopamine during monoamine oxidase inhibition in PC12 cells. Neurochem. Res. 41, 2173–2178.

Goldstein, D.S., Jinsmaa, Y., Sullivan, P., Sharabi, Y., 2017. N-Acetylcysteine prevents the increase in spontaneous oxidation of dopamine during monoamine oxidase inhibition in PC12 cells. Neurochem. Res. 42, 3289–3295.

Goldstein, D.S., Kopin, I.J., Sharabi, Y., 2014. Catecholamine autotoxicity. Implications for pharmacology and therapeutics of Parkinson disease and related disorders. Pharmacol. Ther. 144, 268–282.

Graham, D.G., 1978. Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones. Mol. Pharmacol. 14, 633–643.

Graham, D.G., Tiffany, S.M., Bell Jr., W.R., Gutknecht, W.F., 1978. Autoxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine, and related compounds toward C1300 neuroblastoma cells in vitro. Mol. Pharmacol. 4, 644–653.

Hastings, T.G., Lewis, D.A., Zigmond, M.J., 1996. Role of oxidation in the neurotoxic effects of intrastriatal dopamine injections. Proc. Natl. Acad. Sci. U.S.A. 93, 1956–1961.

Henderson-Smith, A., Fisch, K.M., Hua, J., Liu, G., Ricciardelli, E., Jepsen, K., Huentelman, M., Stalberg, G., Edland, S.D., Scherzer, C.R., Dunckley, T., Desplats, P., 2019. DNA methylation changes associated with Parkinson's disease progression: outcomes from the first longitudinal genome-wide methylation analysis in blood. Epigenetics 14, 365–382.

Herlinger, E., Jameson, R.F., Linert, W., 1995. Spontaneous autoxidation of dopamine. J. Chem. Soc. Perkin Trans. 2, 259–263.

Hernandez-Baltazar, D., Zavala-Flores, L.M., Villanueva-Olivo, A., 2017. The 6-hydroxydopamine model and parkinsonian pathophysiology: novel findings in an older model. Neurologia 32, 533–539.

Hirsch, L., Jette, N., Frolkis, A., Steeves, T., Pringsheim, T., 2016. The incidence of Parkinson's disease: a systematic review and meta-analysis. Neuroepidemiology 46, 292–300.

Ibi, M., Sawada, H., Kume, T., Katsuki, H., Kaneko, S., Shimohama, S., Akaike, A., 1999. Depletion of intracellular glutathione increases susceptibility to nitric oxide in mesencephalic dopaminergic neurons. J. Neurochem. 73, 1696–1703.

Ishibashi, K., Kanemaru, K., Saito, Y., Murayama, S., Oda, K., Ishiwata, K., Mizusawa, H., Ishii, K., 2010. Cerebrospinal fluid metabolite and nigrostriatal dopaminergic function in Parkinson's disease. Acta Neurol. Scand. 122, 46–51.

Ito, S., Fujita, K., 1982. Conjugation of dopa and 5-S-cysteinyldopa with cysteine mediated by superoxide radical. Biochem. Pharmacol. 31, 2887–2889.

Jakubowski, J.L., Labrie, V., 2017. Epigenetic biomarkers for Parkinson's disease: from diagnostics to therapeutics. J. Parkinson's Dis. 7, 1–12.

Jameson, G.N., Zhang, J., Jameson, R.F., Linert, W., 2004. Kinetic evidence that cysteine reacts with dopaminoquinone via reversible adduct formation to yield 5-cysteinyl-dopamine: an important precursor of neuromelanin. Org. Biomol. Chem. 2, 777–782.

Jiménez-Jiménez, F.J., Alonso-Navarro, H., García-Martín, E., Agúndez, J.A., 2014. Cerebrospinal fluid biochemical studies in patients with Parkinson's disease: toward a potential search for biomarkers for this disease. Front. Cell. Neurosci. 8, 369.

Jung, U.J., Kim, S.R., 2018. Beneficial effects of flavonoids against Parkinson's disease. J. Med. Food 21, 421–432.

Jurma, O.P., Hom, D.G., Andersen, J.K., 1997. Decreased glutathione results in calcium-mediated cell death in PC12. Free Radic. Biol. Med. 23, 1055–1066.

Khodadadian, A., Hemmati-Dinarvand, M., Kalantary-Charvadeh, A., Ghobadi, A., Mazaheri, M., 2018. Candidate biomarkers for Parkinson's disease. Biomed. Pharmacother. 104, 699–704.

Kita, T., Asanuma, M., Miyazaki, I., Takeshima, M., 2014. Protective effects of phytochemical antioxidants against neurotoxin-induced degeneration of dopaminergic neurons. J. Pharmacol. Sci. 124, 313–319.

Kujawska, M., Jodynis-Liebert, J., 2018. Polyphenols in Parkinson's disease: a systematic review of in vivo studies. Nutrients 10, E642.
Langston, J.W., 2017. The MPTP story. J. Parkinson's Dis. 7, S11–S19.
Li, H., Dryhurst, G., 2001. Oxidative metabolites of 5-S-cysteinyldopamine inhibit the pyruvate dehydrogenase complex. J. Neural Transm. 108, 1363–1374.
Li, H., Dryhurst, G., 1997. Irreversible inhibition of mitochondrial complex I by benzothiazine-3-carboxylic acid (DHBT-1): a putative nigral endotoxin of relevance to Parkinson's disease. J. Neurochem. 69, 1530–1541.
Li, H., Shen, X.M., Dryhurst, G., 1998. Brain mitochondria catalyze the oxidation of 7-(2-aminoethyl)-3,4-dihydro-5-hydroxy-2H-1,4-benzothiazine-3-carboxylic acid (DHBT-1) to intermediates that irreversibly inhibit complex I and scavenge glutathione: potential relevance to the pathogenesis of Parkinson's disease. J. Neurochem. 71, 2049–2062.
Linert, W., Herlinger, E., Jameson, R.F., Kienzl, E., Jellinger, K., Youdim, M.B., 1996. Dopamine, 6-hydroxydopamine, iron, and dioxygen - their mutual interactions and possible implication in the development of Parkinson's disease. Biochim. Biophys. Acta 1316, 160–168.
Lloyd, K.G., Davidson, L., Hornykiewicz, O., 1975. The neurochemistry of Parkinson's disease: effect of L-dopa therapy. J. Pharmacol. Exp. Ther. 195, 453–464.
Lotharius, J., Brundin, P., 2002a. Impaired dopamine storage resulting from α-synuclein mutations may contribute to the pathogenesis of Parkinson's disease. Hum. Mol. Genet. 11, 2395–2407.
Lotharius, J., Brundin, P., 2002b. Pathogenesis of Parkinson's disease: dopamine, vesicles and α-synuclein. Nat. Rev. Neurosci. 3, 932–942.
Lotharius, J., O'Malley, K.L., 2000. The parkinsonism-inducing drug 1-methyl-4-phenylpyridinium triggers intracellular dopamine oxidation. A novel mechanism of toxicity. J. Biol. Chem. 275, 38581–38588.
Maass, F., Schulz, I., Lingor, P., Mollenhauer, B., Bähr, M., 2018. Cerebrospinal fluid biomarker for Parkinson's disease: an overview. Mol. Cell. Neurosci. S1044–7431, 30352–X.
Magalingam, K.B., Radhakrishnan, A.K., Haleagrahara, N., 2015. Protective mechanisms of flavonoids in Parkinson's disease. Oxid. Med. Cell. Longev. 2015, 314560.
Marchitti, S.A., Deitrich, R.A., Vasiliou, V., 2007. Neurotoxicity and metabolism of the catecholamine-derived 3,4-dihydroxyphenylacetaldehyde and 3,4-dihydroxyphenylglycolaldehyde: the role of aldehyde dehydrogenase. Pharmacol. Rev. 59, 125–150.
Mehta, N.J., Asmaro, K., Hermiz, D.J., Njus, M.M., Saleh, A.H., Beningo, K.A., Njus, D., 2016. Hypochlorite converts cysteinyl-dopamine into a cytotoxic product: a possible factor in Parkinson's Disease. Free Radic. Biol. Med. 101, 44–52.
Meiser, J., Weindl, D., Hiller, K., 2013. Complexity of dopamine metabolism. Cell Commun. Signal. 11, 34.
Monzani, E., Nicolis, S., Dell'Acqua, S., Capucciati, A., Bacchella, C., Zucca, F.A., Mosharov, E.V., Sulzer, D., Zecca, L., Casella, L., 2019. Dopamine, oxidative stress and protein–quinone modifications in Parkinson's and other neurodegenerative diseases. Angew. Chem., Int. Ed. Engl. 58, 6512–6527.
Mor, D.E., Tsika, E., Mazzulli, J.R., Gould, N.S., Kim, H., Daniels, M.J., Doshi, S., Gupta, P., Grossman, J.L., Tan, V.X., Kalb, R.G., Caldwell, K.A., Caldwell, G.A., Wolfe, J.H., Ischiropoulos, H., 2017. Dopamine induces soluble α-synuclein oligomers and nigrostriatal degeneration. Nat. Neurosci. 20, 1560–1568.
Mosca, L., Lendaro, E., d'Erme, M., Marcellini, S., Moretti, S., Rosei, M.A., 2006. 5-S-Cysteinyl-dopamine effect on the human dopaminergic neuroblastoma cell line SH-SY5Y. Neurochem. Int. 49, 262–269.
Mosca, L., Tempera, I., Lendaro, E., Di Francesco, L., D'Erme, M., 2008. Characterization of catechol-thioether-induced apoptosis in human SH-SY5Y neuroblastoma cells. J. Neurosci. Res. 86, 954–960.
Müller, T., Muhlack, S., 2012. Cysteine decrease following acute Levodopa intake in patients with Parkinson's disease. Neurosci. Lett. 521, 37–39.
Mulvihill, K.G., 2019. Presynaptic regulation of dopamine release: role of the DAT and VMAT2 transporters. Neurochem. Int. 122 954-105.
Muñoz, P., Huenchuguala, S., Paris, I., Segura-Aguilar, J., 2012. Dopamine oxidation and autophagy. Parkinson's Dis. 2012, 920953.
Myöhänen, T.T., Schendzielorz, N., Männistö, P.T., 2010. Distribution of catechol-O-methyltransferase (COMT) proteins and enzymatic activities in wild-type and soluble COMT deficient mice. J. Neurochem. 113, 1632–1643.
Navarro-Sánchez, L., Águeda-Gómez, B., Aparicio, S., Pérez-Tur, J., 2018. Epigenetic study in Parkinson's disease: a pilot analysis of DNA methylation in candidate. Cells 7 pii: E150.
Nguyen, M., Wong, Y.C., Ysselstein, D., Severino, A., Krainc, D., 2019. Synaptic, mitochondrial, and lysosomal dysfunction in Parkinson's disease. Trends Neurosci. 42, 140–149.
Parnetti, L., Gaetani, L., Eusebi, P., Paciotti, S., Hansson, O., El-Agnaf, O., Mollenhauer, B., Blennow, K., Calabresi, P., 2019. CSF and blood biomarkers for Parkinson's disease. Lancet Neurol. 18, 573–586.
Pham, A.N., Waite, T.D., 2014. Cu (II)-catalyzed oxidation of dopamine in aqueous solutions: mechanism and kinetics. J. Inorg. Biochem. 137, 74–84.
Pringsheim, T., Jette, N., Frolkis, A., Steeves, T.D., 2014. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov. Disord. 29, 1583–1590.
Rae, C.D., Williams, S.R., 2017. Glutathione in the human brain: review of its roles and measurement by magnetic resonance spectroscopy. Anal. Biochem. 529, 127–143.
Rajabally, Y.A., Martey, J., 2013. Levodopa, vitamins, ageing and the neuropathy of Parkinson's disease. J. Neurol. 260, 2844–2848.
Romagnolo, A., Merola, A., Artusi, C.A., Rizzone, M.G., Zibetti, M., Lopiano, L., 2018. Levodopa-induced neuropathy: a systematic review. Mov. Disord. Clin. Pract. 6, 96–103.
Rosengren, E., Linder-Eliasson, E., Carlsson, A., 1985. Detection of 5-S-cysteinyldopamine in human brain. J. Neural Transm. 63, 247–253.
Sagara, J.I., Miura, K., Bannai, S., 1993. Maintenance of neuronal glutathione by glial cells. J. Neurochem. 61, 1672–1676.
Salauze, L., van der Velden, C., Lagroye, I., Veyret, B., Geffard, M., 2005. Circulating antibodies to cysteinyl catecholamines in amyotrophic lateral sclerosis and Parkinson's disease patients. Amyotroph. Lateral Scler. Other Motor Neuron Disord. 6, 226–233.
Santiago-López, D., Bautista-Martínez, J.A., Reyes-Hernandez, C.I., Aguilar-Martínez, M., Rivas-Arancibia, S., 2010. Oxidative stress, progressive damage in the substantia nigra and plasma dopamine oxidation, in rats chronically exposed to ozone. Toxicol. Lett. 197, 193–200.
Schapira, A.H.V., Chaudhuri, K.R., Jenner, P., 2017. Non-motor features of Parkinson disease. Nat. Rev. Neurosci. 18, 435–450.
Shen, X.-M., Dryhurst, G., 1996. Further insights into the influence of L-cysteine on the oxidation chemistry of dopamine: reaction pathways of potential relevance to Parkinson's Disease. Chem. Res. Toxicol. 9, 751–763.
Shen, X.M., Xia, B., Wrona, M.Z., Dryhurst, G., 1996. Synthesis, redox properties, in vivo formation, and neurobehavioral effects of N- acetylcysteinyl conjugates of dopamine: possible metabolites of relevance relevance to Parkinson's disease. Chem. Res. Toxicol. 9, 1117–1126.
Shen, X.M., Zhang, F., Dryhurst, G., 1997. Oxidation of dopamine in the presence of cysteine: characterization of new toxic products. Chem. Res. Toxicol. 10, 147–155.
Sian, J., Dexter, D.T., Lees, A.J., Daniel, S., Jenner, P., Marsden, C.D., 1994. Glutathione-related enzymes in brain in Parkinson's disease. Ann. Neurol. 36, 356–361.
Sidell, K.R., Olson, S.J., Ou, J.J., Zhang, Y., Amarnath, V., Montine, T.J., 2001. Cysteine and mercapturate conjugates of oxidized dopamine are in human striatum but only the cysteine conjugate impedes dopamine trafficking in vitro and in vivo. J. Neurochem. 79, 510–521.
Smeyne, M., Smeyne, R.J., 2013. Glutathione metabolism and Parkinson's disease. Free Radic. Biol. Med. 62, 13–25.
Solano, F., Hearing, V.J., García-Borrón, J.C., 1999. Neurotoxicity due to o-Quinones: neuromelanin formation and possible mechanisms for o-Quinone detoxification. Neurotox. Res. 1, 153–169.
Sossi, V., de La Fuente-Fernandez, R., Holden, J.E., Doudet, D.J., McKenzie, J., Stoessl, A.J., Ruth, T.J., 2002. Increase in dopamine turnover occurs early in Parkinson's disease: evidence from a new modeling approach to PET 18 F-fluorodopa data. J. Cereb. Blood Flow Metab. 22, 232–2399.
Spencer, J.P.E., Whiteman, M., Jenner, P., Halliwell, B., 2002. 5-S-cysteinyl-conjugates of catecholamines induce cell damage, extensive DNA base modification and increases in caspase-3 activity in neurons. J. Neurochem. 81, 122–129.
Stokes, A.H., Hastings, T.G., Vrana, K.E., 1999. Cytotoxic and genotoxic potential of dopamine. J. Neurosci. Res. 55, 659–665.
Subramaniam, S.R., Chesselet, M.F., 2013. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Prog. Neurobiol. 106–107, 17–32.
Sulzer, D., Bogulavsky, J., Larsen, K.E., Behr, G., Karatekin, E., Kleinman, M.H., Turro, N., Krantz, D., Edwards, R.H., Greene, L.A., Zecca, L., 2000. Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles. Proc. Natl. Acad. Sci. U.S.A. 97, 11869–11874.
Sulzer, D., Zecca, L., 2000. Intraneuronal dopamine-quinone synthesis: a review. Neurotox. Res. 1, 181–195.
Sun, Y., Pham, A.N., Hare, D.J., Waite, T.D., 2018. Kinetic modeling of pH-dependent oxidation of dopamine by iron and its relevance to Parkinson's disease. Front. Neurosci. 12, 859.
Titova, N., Padmakumar, C., Lewis, S.J., Chaudhuri, K.R., 2017. Parkinson's: a syndrome rather than a disease? J. Neural Transm. 124, 907–914.
Tse, D.C., McCreery, R.L., Adams, R.N., 1976. Potential oxidative pathways of brain catecholamines. J. Med. Chem. 19, 37–40.
van Heesbeen, H.J., Smidt, M.P., 2019. Entanglement of genetics and epigenetics in Parkinson's disease. Front. Neurosci. 13, 277.
Vauzour, D., Corona, G., Spencer, J.P., 2010. Caffeic acid, tyrosol and p-coumaric acid are potent inhibitors of 5-S-cysteinyl-dopamine induced neurotoxicity. Arch. Biochem. Biophys. 501, 106–111.
Vauzour, D., Pinto, J.T., Cooper, A.J., Spencer, J.P., 2014. The neurotoxicity of 5-S-cysteinyldopamine is mediated by the early activation of ERK1/2 followed by the subsequent activation of ASK-1/JNK1/2 pro-apoptotic signalling. Biochem. J. 463, 41–52.
Vauzour, D., Ravaioli, G., Vafeiadou, K., Rodriguez-Mateos, A., Angeloni, C., Spencer, J.P.E., 2008. Peroxynitrite induced formation of the neurotoxins 5-S-cysteinyl-dopamine and DHBT-1: implications for Parkinson's disease and protection by polyphenols. Arch. Biochem. Biophys. 476, 145–151.
Vauzour, D., Vafeiadou, K., Spencer, J.P.E., 2007. Inhibition of the formation of the neurotoxin 5-S-cysteinyl-dopamine by polyphenols. Biochem. Biophys. Res. Commun. 362, 340–346.
Vergo, S., Johansen, J.L., Leist, M., Lotharius, J., 2007. Vesicular monoamine transporter 2 regulates the sensitivity of rat dopaminergic neurons to disturbed cytosolic dopamine levels. Brain Res. 1185, 18–32.
Villar-Pique, A., Lopes da Fonseca, T., Outeiro, T.F., 2016. Structure, function and toxicity of alpha-synuclein: the Bermuda triangle in synucleinopathies. J. Neurochem. 139 (Suppl. 1), 240–255.
Whitehead, R.E., Ferrer, J.V., Javitch, J.A., Justice, J.B., 2001. Reaction of oxidized dopamine with endogenous cysteine residues in the human dopamine transporter. J. Neurochem. 76, 1242–1251.
Wong, Y.C., Krainc, D., 2017. α-Synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies. Nat. Med. 23, 1–13.
Xin, W., Shen, X.M., Li, H., Dryhurst, G., 2000. Oxidative metabolites of 5-S-cysteinylnorepinephrine are irreversible inhibitors of mitochondrial complex I and the alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase complexes: possible

implications for neurodegenerative brain disorders. Chem. Res. Toxicol. 13, 749–760.
Yaping, S., Weidong, L., 2019. Recent advances and perspectives of metabolomics-based investigations in Parkinson's disease. Mol. Neurodegener. 14, 3.
Yoshimoto, Y., Nakaso, K., Nakashima, K., 2005. L-DOPA and dopamine enhance the formation of aggregates under proteasome inhibition in PC12 cells. FEBS Lett. 579, 1197–1202.
Yu, R.L., Tan, C.H., Lu, Y.C., Wu, R.M., 2016. Aldehyde dehydrogenase 2 is associated with cognitive functions in patients with Parkinson's disease. Sci. Rep. 6, 30424.
Zafar, K.S., Siegel, D., Ross, D., 2006. Potential role for cyclized quinones derived from dopamine, DOPA, and 3,4-dihydroxyphenylacetic acid in proteasomal inhibition. Mol. Pharmacol. 70, 1079–1086.
Zeevalk, G.D., Razmpour, R., Bernard, L.P., 2008. Glutathione and Parkinson's disease: is this the elephant in the room? Biomed. Pharmacother. 62 236–24.
Zhang, F., Dryhurst, G., 1994. Effects of L-cysteine on the oxidation chemistry of dopamine. J. Med. Chem. 37, 1084–1098.
Zhang, F., Dryhurst, G., 1995a. Reactions of cysteine and cysteine derivatives with dopamine-o-quinone and further in- sights into the oxidation chemistry of 5-S-cysteinyldopamine: potential relevance to idiopathic Parkinson's disease. Bioorg. Chem. 23, 193–216.
Zhang, F., Dryhurst, G., 1995b. Influence of glutathione on the oxidation chemistry of the catecholaminergic neurotransmitter dopamine. J. Electroanal. Chem. Interfacial Electrochem. 398, 117–128.