Mechanisms of Dopamine Oxidation and Parkinson's Disease

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Abstract

Dopamine's ability to oxidize to aminochrome explains why this molecule may be a neurotoxic compound that induces toxicity in both cell lines and animal models. Spontaneous dopamine oxidation is prevented by vesicular monoaminergic transporter-2 (VMAT-2) that takes up dopamine into the monoaminergic synaptic vesicles where the low pH prevents dopamine oxidation. Dopamine in the cytosol can also be degraded by monoamine oxidase (MAO) and catechol ortho-methyl transferase (COMT) soluble isoform. However, under certain unknown conditions dopamine oxidize to aminochrome, the precursor of neuromelanin, pigment found in the human substantia nigra. Aminochrome participates in two neurotoxic reactions: (i) the one-electron reduction of aminochrome, which is catalyzed by flavoenzymes that use NADH or NADPH as electron donors. This reaction produces leukoaminochrome-*o*-semiquinone radical, which is extremely reactive with oxygen that autoxidizes depleting both NADH and O_2 required for ATP synthesis; and (ii) aminochrome forms adducts with proteins such as alpha synuclein. In addition, aminochrome inactivates mitochondrial complex I of electron transport chain, vacuolar H-type ATPase, actin, and α- and β-tubulin disrupting the cytoskeleton network. Aminochrome is also able to participate in three neuroprotective reactions: (i) polymerization to neuromelanin; (ii) aminochrome two-electron reduction to leukoaminochrome catalyzed by DT-diaphorase; and (iii) glutathione conjugation of aminochrome catalyzed by glutathione S-transferase M2-2. Aminochrome's role in the degeneration of dopaminergic neurons in Parkinson's disease is discussed. Aminochrome may induce the focal neurodegeneration of dopaminergic neurons through mechanisms involving cytoskeleton dysfunction, mitochondrial dysfunction, protein aggregation, oxidative stress, neuroinflammation, endoplasmic reticulum stress, and protein degradation dysfunction.

Keywords

Aminochrome · Dopamine · DT-diaphorase · Glutathione S-transferase M2-2 · Metabolism · Neurotoxicity · Neurotoxins · Orthoquinones · Oxidation · Parkinson's disease

Abbreviations

AADC	Aromatic amino acid decarboxylase
COMT	Catechol ortho-methyltransferase
GST M2-2	Glutathione S-transferase M2-2
L-dopa	L-dihydroxyphenylanaline
MAO	Monoamine oxidases
TH	Tyrosine hydroxylase
VMAT-2	Vesicular monoaminergic transporter-2

1 Dopamine

1.1 Dopamine Synthesis

Dopamine is an essential neurotransmitter synthetized by central and periphery nervous systems. It is well recognized for its role as neuromodulator for movement control among other functions (Gvirts Probolovski & Dahan, 2021). The release of dopamine from dopaminergic neurons is a normal event that plays an essential role in human body motor activity. Dopamine is synthetized in dopaminergic neurons by using the amino acid tyrosine as precursor where this pathway requires the catalytic action of tyrosine hydroxylase and aromatic amino acid decarboxylase. Tyrosine hydroxylase catalyzes the conversion of tyrosine to L-dihydroxyphenylanaline (L-dopa), that is, it is an enzymatic reaction dependent of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4) (Flydal et al., 2021) and the rate-limiting step in dopamine synthesis (Levitt et al., 1965).

Aromatic amino acid decarboxylase catalyzes the decarboxylation of L-dopa to dopamine and CO_2. Interestingly, dopamine is stored in monoaminergic synaptic vesicles because the dopamine transporter (vesicular monoaminergic transporter-2, VMAT-2) is expressed in the membrane and mediates VMAT-2-dependent dopamine uptake (Magee et al., 2020). Dopamine has a catechol structure where the hydroxyl groups are dissociated at physiological pH of dopaminergic neurons and can be oxidized by the catechol structure to ortho-quinones, which can be neurotoxic. Interestingly, dopamine synthesis enzymes, tyrosine hydroxylase and aromatic amino acid decarboxylase, are associated with VMAT-2 forming a kind of complex, which prevents the formation of free dopamine (Cartier et al., 2010).

The dopamine uptake mediated by VAMT-2 is associated with a vesicular ATPase that is translocated into the vesicles as ATP is hydrolyzed to ADP, Pi, and one proton (H^+). This process creates a proton gradient (Fig. 1). The VMAT-2 transporter exports two protons as one molecule of dopamine is taken into the cell (Chaudhry et al., 2008; Knoth et al., 1981). The pH inside the monoaminergic synaptic vesicles has been estimated to be 2 to 2.4 pH units lower than the pH in the cytosol (Guillot & Miller, 2009). Dopamine vesicular uptake efficiency may be regulated by SLC10A4, vesicular monoaminergic associated transporter than no display activity as dopamine transporter. Orphan transporter SCL10A4 contributes to acidification in synaptic vesicles (Larhammar et al., 2015). The dopamine inside the monoaminergic synaptic vesicles is stable. It does not oxidize to *o*-quinone because it is well protonated. Another source of dopamine in dopaminergic neurons is dopamine released under neurotransmission that dopamine transporter takes up into the cytosol. Interestingly, dopamine transporter, synaptogyrin-3, and VMAT-2 form a kind of complex, preventing the release of intracellular free dopamine in the cytosol (Egaña et al., 2009).

The free dopamine in the cytosol participates in three reactions. First, the dopamine can undergo oxidative deamination to 3,4-dihydroxyphenylacetaldehyde by

monoamine oxidases. Second, the dopamine catechol structure can be oxidized to become aminochrome. Finally, dopamine can be methylated by ortho methyltransferases (Fig. 1).

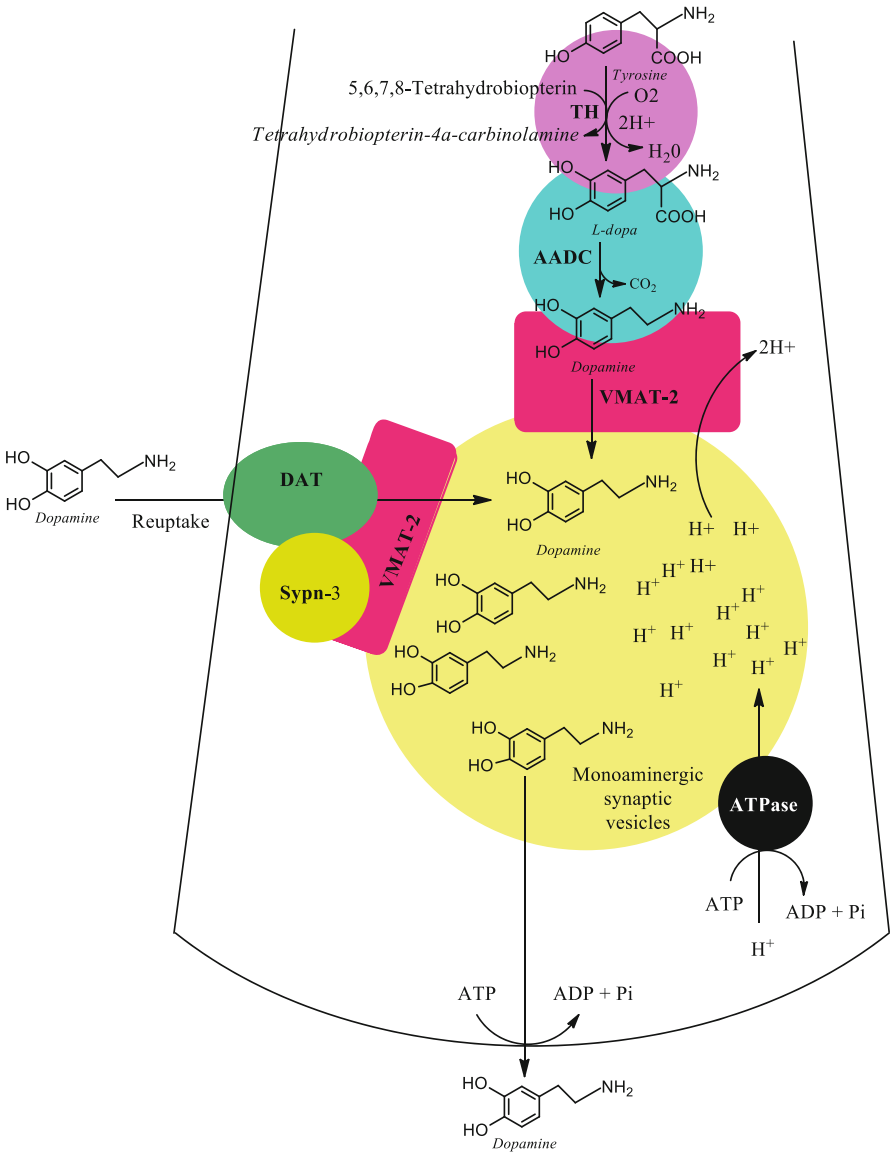

Fig. 1 Dopamine synthesis from tyrosine catalyzed by tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase (AADC) and uptake into monoaminergic synaptic vesicles mediated by VMAT-2

1.2 Regulation of Dopamine Synthesis

The synthesis of dopamine is controlled at different levels. The activity, expression, and location subcellular of the enzymes that participate in its synthesis play an important role. Tyrosine hydroxylase is the main enzyme regulating the synthesis of dopamine. This catalyzes the rate-limiting step of synthesis dopamine (Levitt et al., 1965). TH is regulated by complex processes such as transcriptional mechanisms, proteasome degradation, phosphorylation, protein-protein interactions, and changes in intracellular localization (see review Tekin et al., 2014). PTEN-induced putative kinase 1 (PINK1) and DJ-1 regulate tyrosine hydroxylase expression and dopamine synthesis (Takahashi-Niki et al., 2017; Lu et al., 2018; Xu et al., 2020). In turn, its activity is controlled by protein phosphorylation (see review Dunkley & Dickson, 2019) and some metabolites such as salsolinol (Briggs et al., 2013). Moreover, TH subcellular localization to synaptic vesicles may be modulated by THSer (P)-31 phosphorylation and its interaction with heat shock cognate protein 70 (Hsc70) (Parra et al., 2016; Jorge-Finnigan et al., 2017).

Apparently, regulation of TH expression and activity occurs in Parkinson's disease patients. Selective loss of isoform 1 and increased isoform 2 was observed in Parkinson's disease brains. Regulation of TH activity by phosphorylation could be a compensatory mechanism to counteract the dopamine deficit in terminal field regions (Shehadeh et al., 2019).

2 Dopamine Degradation

2.1 The Oxidative Deamination of Dopamine

Monoamine oxidase (MAO, E.C. 1.4.3.4) catalyzes the oxidative deamination of different amines and neurotransmitters. The monoamine oxidases degrade excess dopamine in the cytosol (Jones & Raghanti, 2021) by catalyzing the oxidative deamination of the dopamine amino group to 3,4-dihydroxyphenylacetaldehyde. Ammonia and hydrogen peroxide are also produced in this reaction. 3,4-Dihydroxyphenylacetaldehyde is metabolized by aldehyde dehydrogenase to 3,4-dihydroxyphenylacetic acid (DOPAC) as NAD^+ is simultaneously reduced to NADH (Fig. 2). The MAO enzymes are flavoenzymes with multiple isoforms. The isozymes are labeled A and B and share 70% identity. These enzymes carry sequences specific to FAD (Bach et al., 1988; Murugan et al., 2020) and are localized to the outer membranes of the mitochondria and with a little microsomal fraction, in neurons, glial cells, immune cells, cancer cells, and other cell types (Weyler et al., 1990; Shih et al., 1997; Dhabal et al., 2018). MAO-A is mainly found in catecholaminergic neurons, whereas MAO-B is found in serotonergic and histaminergic neurons as well as in astrocytes (Westlund et al., 1988; Saura et al., 1994; Saitoh et al., 2021). MAO-A acts on mainly monoaminergic neurotransmitters such as serotonin, dopamine, noradrenaline, and adrenaline. In contrast, the substrates of MAO-B include trace amines such as tyramine and phenylethylamine

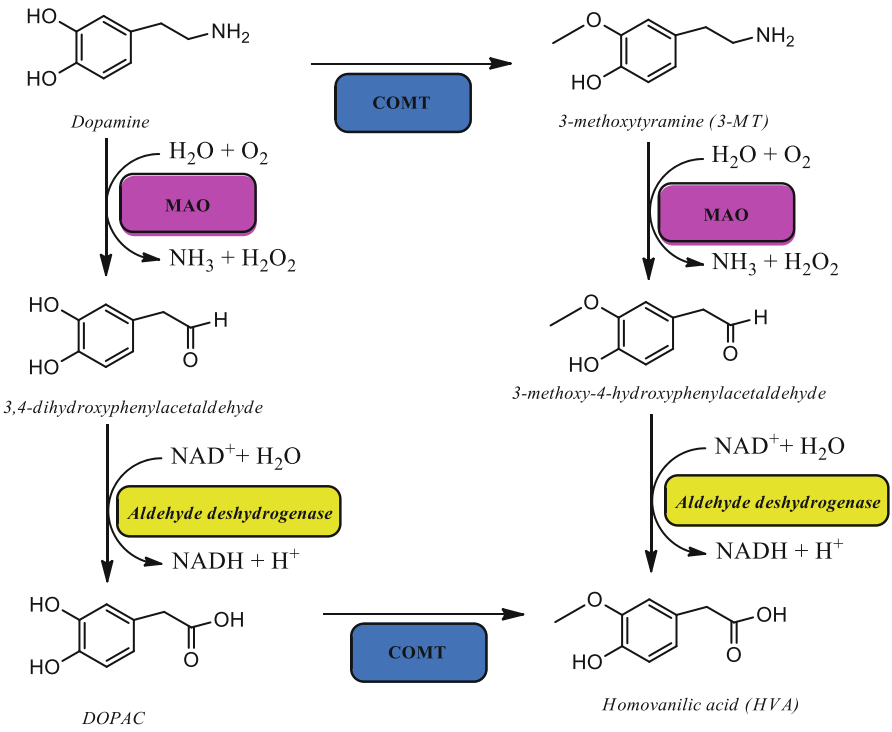

Fig. 2 Dopamine degradation catalyzed by monoamine oxidase (MAO) and catechol ortho-methyl transferase (COMT)

(Strolin Benedetti et al., 1992). Interestingly, it was described that each MAO subtype modulates the activity and expression of the other isoenzyme. Similarly, MAO polymorphisms or mutations and polymorphisms of regulatory protein such as parkin, sirtuin 1, forkhead box O (FOXO), among others, also affects its expression (Naoi et al., 2016). MAO seems be related with the development of various neuropsychiatric disorders such as Parkinson's disease and depression, and also other diseases, coronary artery disease and diabetes (Lighezan et al., 2016; Duarte et al., 2021). Given MAO's role in dopamine and serotonin degradation and its ability to induce oxidative stress, several research efforts are aimed at the discovery of selective, reversible, and potent MAO inhibitors with lower side effect. Thus, several compounds have been developed as MAO inhibitors. First-generation non-selective inhibitors of MAO include isocarboxazid, phenelzine, nialamide, iproniazid, iproclozide, ladostigil, and tranylcypromine. Second generation of selective irreversible inhibitors of MAO include clorgyline for MAO-A, and selegiline and rasagiline for MAO-B. Third generation of selective irreversible inhibitors of MAO include brofaromine, moclobemide, pirlindole, CX157, harmine, methylene blue for MAO-A and zonisamide and safinamide for MAO-B (for reviews, see Hong & Li, 2018; Duarte et al., 2021). Study on the efficacy of MAO-B inhibitors in patients

with Parkinson's disease showed that combination therapy with MAO-B inhibitors and Levodopa and selegiline was more effective than rasagiline and safinamide (Binde et al., 2018). The MAO in dopaminergic neurons degrades dopamine to maintain low cytosolic concentrations and to prevent dopamine oxidation. However, MAO activity is associated with oxidative stress. This process is a result of hydrogen peroxide formation from the oxidative deamination of dopamine (Duarte et al., 2021). Hydrogen peroxide is a precursor to the hydroxyl radical. Rasagiline or coumarin-rasagiline hybrids may protect the brain in Parkinson's disease model systems by inhibiting the formation of reactive oxygen species derived from the deaminative oxidation of dopamine catalyzed by MAO-B (Weinreb et al., 2011; Matos et al., 2020). New studies revealed interesting neuroprotective and anti-apoptotic properties of selegiline and rasagiline (Szökő et al., 2018; Tábi et al., 2020). Although several studies have shown a relationship between high levels of MAO-B and Parkinson's disease (Mallajosyula et al., 2008; Li et al., 2014), others describe that MAO-B levels were not increased, and there were no loss of the MAO-A in the substantia nigra of Parkinson's disease. This opens a debate whether the suppression of these enzymes may influence the progression of parkinsonian disorders (Tong et al., 2017).

2.2 Ortho-Methylation of Dopamine

Dopamine is also degraded by catechol ortho-methyltransferase (COMT; EC 2.1.1.6). This enzyme converts dopamine to 3-methoxytyramine, which is then metabolized to 3-methoxy-4-hydroxyphenylacetaldehyde by MAO. Finally, homovanillic acid is formed when aldehyde dehydrogenase catalyzes the oxidation of 3-methoxy-4-hydroxyphenylacetaldehyde (Fig. 2). NADH is also formed in this reaction. Homovanillic acid is also formed by COMT-mediated methylation of the hydroxyl group on DOPAC. COMT is present in different tissues such as the blood, liver, kidney, heart, and brain (Xia et al., 2020; Azhar et al., 2020; Börzsei et al., 2021; Ni et al., 2021). Two isoforms of COMT have been discovered: the first is the soluble isoform S-COMT, and the second is the membrane-bound isoform MB-COMT, involved in dopamine brain metabolism (Su et al., 2021). Both the S- and MB-COMT isoforms are found in microglial and astroglia cells. COMT is present in pyramidal neurons, cerebellar Purkinje, and granular cells and striatal spiny neurons (Myöhänen et al., 2010). MB-COMT is localized to the cell body, axons, and dendrites of rat cortical neurons. The C-terminal catalytic domain of MB-COMT is in the extracellular space. This domain inactivates the synaptic and extra synaptic dopamine in presynaptic and postsynaptic neurons (Chen et al., 2011). Recent studies showed that MB-COMT is the dominant isoform for metabolism dopamine in PC12 cells and rat brain (Su et al., 2021). Whereas MB-COMT deficient mice showed higher extracellular dopamine levels in the striatum, but without changes in total COMT activity in the brain, its function cannot be entirely substituted by S-COMT (Tammimaki et al., 2016, 2018). This enzyme is associated with different pathologies such as cancer, obesity, and neuropsychiatric disorders

(Tolba et al., 2019; Fornes et al., 2019; Ni et al., 2021). Its expression can be modulated by different molecules. The downregulation of COMT by estrogen most severely affects the prefrontal cortex and kidneys, where COMT is physiologically important for dopamine metabolism (Schendzielorz et al., 2011). Increased nuclear factor-kappa B (NF-κB) activity also downregulates the expression of COMT in forebrain and midbrain structures inactivating catecholamines that cause inflammatory pain (Hartung et al., 2015). COMT is downregulated in stressful conditions, but not chronic stress. This effect is associated with resilience to stress and is modulated by dopaminergic pathways (Kovalenko et al., 2016; Azadmarzabadi et al., 2018). By contrary, a major increase in catechol-*O*-methyltransferase expression in the locus coeruleus of Pink1 deficient rat model of Parkinson's disease supporting the hypothesis that early-stage Parkinson's disease includes noradrenergic loss in the brainstem (Kelm-Nelson et al., 2018). Different COMT inhibitors have been developed over time being classified as the first generation, second generation, and novel compounds. COMT inhibitors are co-adjuvant drugs applied in Parkinson's disease with potential therapeutic benefits in various neurological disorders (for reviews, see Akhtar et al., 2020). Entacapone, selective inhibitor of second generation, has been applied to inhibit COMT in Parkinson's disease treatment (Pinheiro et al., 2019). This inhibition prolongs the half-life of L-dopa and allows the delivery of continuous stimulation to the neuronal dopaminergic receptors (Marin & Obeso, 2010). Entacapone-induced inhibition of colon motility in Parkinson's disease rat was also observed (Li et al., 2015). Several COMT genotypes at SNPs such as rs4818, rs4680, rs165728, and rs174699 have been described, but not all of them are functional and affect enzyme activity. A systematic review and meta-analyses evidence that Val158Met polymorphism (rs4680) alter activity and expression protein (Tunbridge et al., 2019; Dean et al., 2020; Zhao et al., 2020). Studies suggest that the COMT genotype may influence the therapeutic potential of COMT inhibitors and also levodopa response variability in Parkinson's disease (Barkus et al., 2016; Zhao et al., 2020).

3 Dopamine Oxidation to Ortho-Quinones

3.1 Dopamine Oxidation to Aminochrome

The protons on the dopamine hydroxyl groups are dissociated when dopamine is in the cytosol (pH 7.4). Dopamine spontaneously oxidizes to neuromelanin in the presence of oxygen, even in the absence of metal-ion catalysts (Linert et al., 1996; Pham & Waite, 2014; Hedges et al., 2020). Dopamine oxidation can produce a dopamine *o*-semiquinone radical and a superoxide radical (reaction 1, Fig. 3). Two dopamine *o*-semiquinone radicals can react in a disproportionation reaction to produce one molecule of dopamine *o*-quinone and one molecule of dopamine (reaction 2, Fig. 3). Alternatively, the dopamine *o*-semiquinone radical can be one-electron oxidized by oxygen to produce dopamine *o*-quinone and a superoxide radical (reaction 3, Fig. 3). Dopamine oxidation can also be catalyzed by metals and

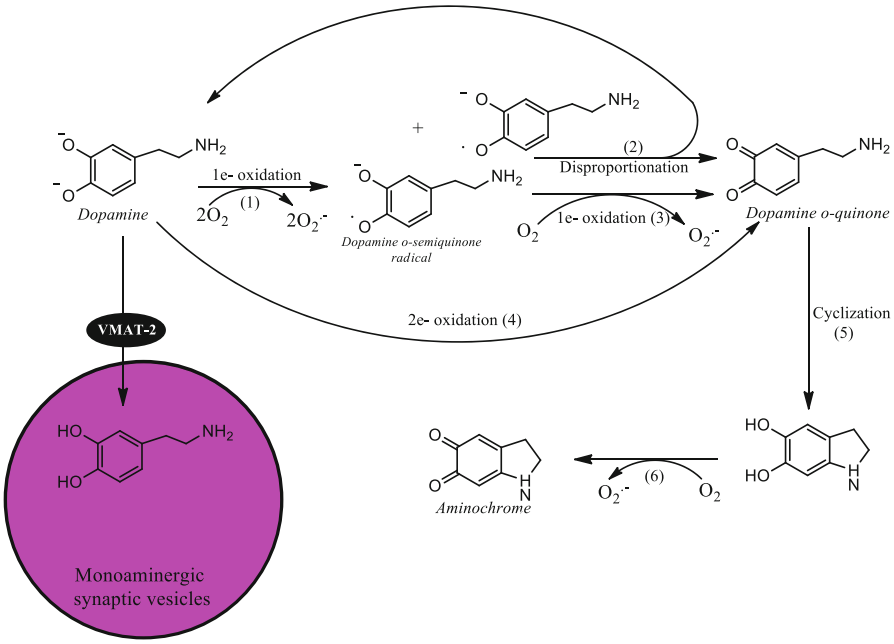

Fig. 3 Dopamine oxidation to aminochrome

hypochlorous acid. Manganese (III) oxidizes dopamine under aerobic and anaerobic conditions without forming superoxide radicals because manganese (III) catalyzes the formation of both dopamine *o*-semiquinone and dopamine *o*-quinone (Segura-Aguilar & Lind, 1989). Copper sulfate (II) and iron chloride (III) oxidize dopamine by forming a complex with it (Paris et al., 2001, 2005). Sodium metaperiodate also catalyzes dopamine oxidation (Graham et al., 1978). Hypochlorous acid reaction with dopamine forms dopamine *o*-quinone. Calcium cation affects the dopamine oxidation pathway due the chelating effect of semiquinone formed (Palladino et al., 2020). Further, prostaglandin H synthase, lactoperoxidase, cytochrome P450, xanthine oxidase, and dopamine β-monooxygenase catalyze dopamine oxidation through peroxidase activity (Galzigna et al., 2000; Thompson et al., 2000; Segura-Aguilar, 1996; Foppoli et al., 1997; Hastings, 1995). Tyrosinase can catalyze the two-electron oxidation of dopamine to dopamine *o*-quinone (reaction 4, Fig. 3). This process does not form dopamine *o*-semiquinone radicals or consume oxygen (Segura-Aguilar et al., 1998; Jimenez et al., 1984).

Dopamine *o*-quinone is only stable at a pH below 2.0. Thus, this molecule is not stable at physiological pH (Segura-Aguilar & Lind, 1989). The amino group of dopamine *o*-quinone spontaneously rearranges and undergoes cyclization at the rate of 0.15 s^{-1} (Tse et al., 1976) to become leukoaminochrome (reaction 5, Fig. 3). The rate-limiting step of this reaction is the formation of a hydroxide ion from a water molecule. This reaction shows a strong dependency on the pH value (Umek et al., 2018; Salomäki et al., 2018). Later, leukoaminochrome undergoes oxidation to

become aminochrome (reaction 6, Fig. 3). Purified aminochrome is stable for approximately 3 h (Paris et al., 2010). This timeframe suggests that aminochrome is the relevant final product of dopamine oxidation in neuromelanin-containing dopaminergic neurons.

Aminochrome formation is dependent on the presence of free cytosolic dopamine that can be oxidized. However, the existence of free dopamine in cytosol that can be oxidized to ortho-quinones (dopamine *o*-quinone, aminochrome, and 5,6-indolequinone) is prevented by the existence of three mechanisms: (i) the formation of a kind of complex between VMAT-2, tyrosine hydroxylase, and aromatic amino acid decarboxylase that prevents the release of free dopamine during the synthesis of dopamine from the amino acid tyrosine since tyrosine is converted to L-dopa which is immediately converted into dopamine that VMAT-2 transports to the monoaminergic synaptic vesicles (Cartier et al., 2010); (ii) another source of free dopamine in the cytosol in dopaminergic neurons is the reuptake of dopamine released during neurotransmission where the dopamine transporter takes up dopamine into the cytosol. However, the dopamine transporter forms a kind of complex with synaptogyrin-3, and VMAT-2 that prevents the release of free dopamine into the cytosol (Egaña et al., 2009); and (iii) if these two previous mechanisms fail, the MAO enzyme catalyzes the degradation of dopamine. Another strategy to prevent the oxidation of dopamine is dopamine release partially from synaptic vesicles by ensuring their faster reacidification possibly reflecting a presynaptic adaptation mechanism (Gu et al., 2015). However, under certain conditions, free dopamine in the cytosol can oxidize to form aminochrome. The above is supported by discovered that the nonenzymatic dopamine oxidation reaction is comparably as fast as enzymatic dopamine oxidation reaction (Umek et al., 2018). The presence of neuromelanin in the substantia nigra of healthy controls suggests that dopamine oxidation occurs in vivo because neuromelanin increase with the age in human (Zecca 2002).

3.2 Aminochrome Tautomerization

Aminochrome is an unstable molecule that rearranges to 5,6-dihydroxyindole (reaction 1, Fig. 4), which is then oxidized to become 5,6-indolequinone (reaction 2, Fig. 4) (Napolitano et al., 2011). However, tyrosinase-catalyzed dopamine oxidation in the absence of metals produces aminochrome that is stable for 3 h after purification (Paris et al., 2010). Another study performed with nuclear magnetic resonance spectroscopy revealed that aminochrome is stable during 40 min before it is rearrangement to 5,6-indolequinone (Bisaglia et al., 2007). From a physiological point of view, 40 min is adequate for a molecule to be one- or two-electron reduced by flavoenzymes or to form adducts with proteins. The 5,6-indolequinone is in equilibrium with the quinone methide even though the presence of transition metal cations favors the formation of the quinone methide (reaction 3, Fig. 4). The quinone methide is also in equilibrium with quinonimine (reaction 4, Fig. 4; Pezzella et al., 2007). It has been reported the formation of dopaminochrome during dopamine oxidation but the structure of this ortho-quinone is unknown (Linsenbardt et al., 2009, 2012)

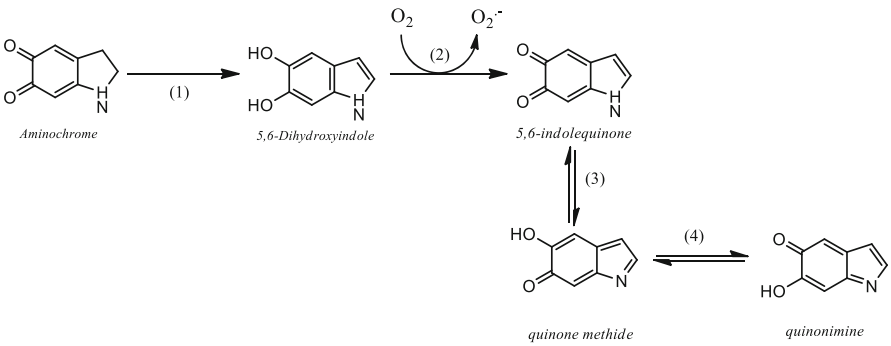

Fig. 4 Aminochrome tautomerization

Dopaminochrome is not aminochrome because these two ortho-quinones have different absorption maximum where dopaminochrome has an absorption maximum of 303 and 479 nm (Ochs et al., 2005). Therefore, dopaminochrome possible corresponds to 5,6-indolequinone or an unidentified *o*-quinone.

4 Aminochrome Metabolism

4.1 Aminochrome Polymerization to Neuromelanin

Aminochrome is not completely stable. At high concentrations, it polymerizes to form a dark pigment called neuromelanin (Fig. 5). Neuromelanin formation appears to be a normal process because it is present in dopaminergic neurons of the substantia nigra in healthy subjects without Parkinson's disease. It accumulates with age (Zecca et al., 2002). In vivo studies describe that the neuromelanin increased with age is strongly pronounced from childhood to adolescence, reaching a plateau phase in the middle age and later declining in older age (Xing et al., 2018). Neuromelanin appears to have a neuroprotective function through the chelation of metals such as iron, calcium, among others (Gerlach et al., 2003; Hong & Simon, 2007; Zucca et al., 2017; Knörle, 2018), and the binding of proteins such as alpha-synuclein (Fasano et al., 2006). However, it has been also suggested that the interaction of neuromelanin with alpha-synuclein is cytotoxic (Xu & Chan, 2015). Neuromelanin induces apoptosis in cell cultures (Naoi et al., 2008). Interestingly, extracellular neuromelanin also induces microglial activation in the substantia nigra. As a result of this process, superoxide radicals, nitric oxide, hydrogen peroxide, and pro-inflammatory factors are produced. Therefore, selective loss of dopaminergic neurons by showing decreased dopamine uptake and lower numbers and shorted dendrites are observed (Zhang et al., 2011, 2013). Microglia activation by neuromelanin appears to be caspase dependent (Viceconte et al., 2015). However, neuromelanin is normally stored in double-membrane vacuoles, and the possible neurotoxic effects described by Zhang are avoided.

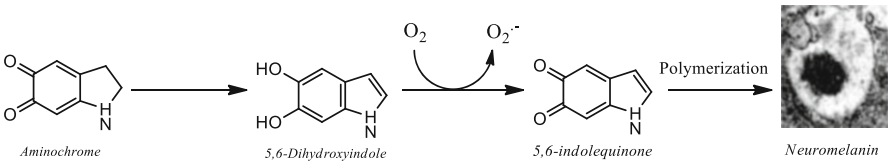

Fig. 5 Aminochrome as precursor of neuromelanin pigment

4.2 Aminochrome Adducts with Proteins

Aminochrome forms adducts with proteins such as alpha synuclein that may be involved in the pathogenesis of Parkinson's disease. Alpha-synuclein is an abundant brain protein. It was found linked to presynaptic vesicles having key role in synaptic function. High expression of alpha-synuclein is detected in brain regions that are seen affected in Parkinson's disease (Taguchi et al., 2019). Insoluble aggregates of alpha-synuclein form part of Lewy bodies in sporadic Parkinson's disease (Baba et al., 1998). Alpha-synuclein oligomers are also visualized in post-mortem brain tissue from patients with Parkinson's disease (Roberts et al., 2015). Alpha-synuclein is hypothesized to cause damage through the generation of neurotoxic protofibrils and has been associated with familial Parkinson's disease. Although its primary function appears to be involved in the neurotransmitter release, by regulating storage, release, and presynaptic vesicle cycling (Calo et al., 2016), the role of alpha-synuclein in sporadic Parkinson's disease remains an open question. However, aminochrome forms adducts with alpha-synuclein (Fig. 6). This process induces the formation of neurotoxic protofibrils that may play a key role in alpha-synuclein neurotoxicity (Conway et al., 2001; Muñoz et al., 2015). Aminochrome induces the formation of alpha synuclein oligomers (Cardenas et al., 2008; Muñoz et al., 2015) like 3,4-dihydroxyphenylacetaldehyde (DOPAL) (Jinsmaa et al., 2020). Interestingly, while aminochrome alpha-synuclein oligomers are neurotoxic (Muñoz et al., 2015), novel aminochrome glutathione alpha-synuclein oligomers are also formed without demonstrable toxicity (Huenchuguala et al., 2019). Therefore, aminochrome may be the link between alpha-synuclein and sporadic Parkinson's disease. In familial Parkinson's disease, the formation of neurotoxic protofibrils is dependent on the presence of a specific point mutation that changes alpha-synuclein properties (Polymeropoulos et al., 1997). Recently, new familial alpha-Syn mutation (A53E) has been discovered which was associated with larger population of oligomers and more aggressive form of familial Parkinson's disease (Mohite et al., 2018). In sporadic Parkinson's disease, however, the formation of neurotoxic protofibrils is dependent on the formation of aminochrome. The aminochrome forms adduct with other proteins such as actin and α- and β-tubulin and disrupt cytoskeletal architecture (Fig. 6; Paris et al., 2010). The adduct formation between aminochrome and tubulin was responsible for microtubules instability and the inhibition of their assembly (Briceño et al., 2016). Dopamine *o*-quinone, a transient precursor of aminochrome at physiological pH, forms adduct with and inactivates parkin, a ubiquitin ligase of the proteasomal system (LaVoie et al., 2005). Aminochrome inactivates the proteasomal

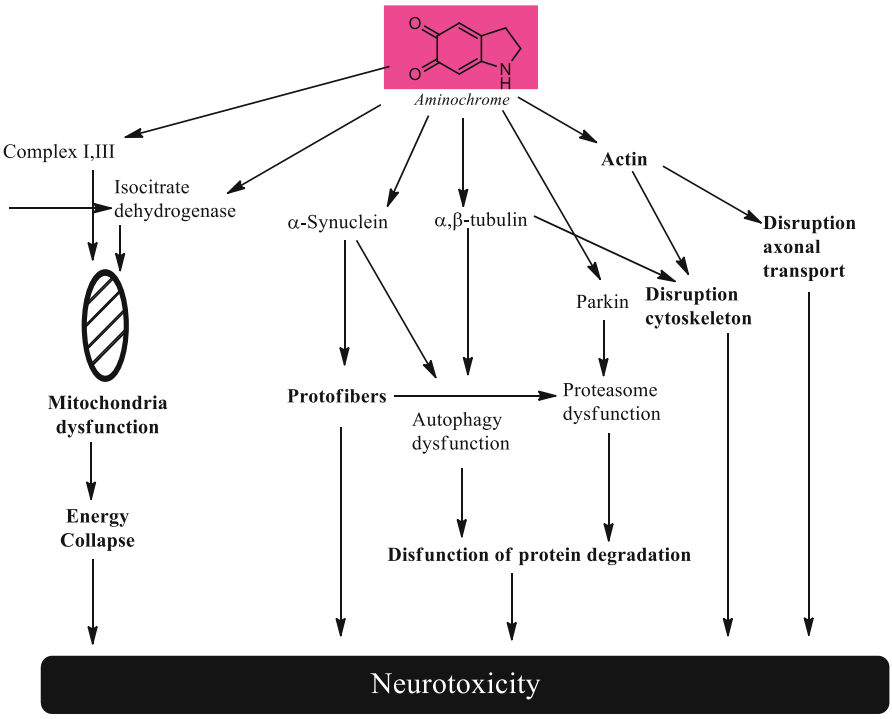

Fig. 6 Formation of aminochrome adducts with proteins

system (Zafar et al., 2006). Interestingly, a mutation in the parkin gene has also been associated with a familial form of juvenile Parkinson's disease (Kitada et al., 1998). Dopamine *o*-quinone forms adduct with the L-lactate dehydrogenase (LDH), malate dehydrogenase (MDH) (Yu et al., 2015), and mitochondrial complex I (Van Laar et al., 2009) and induces energy collapse by inactivating mitochondrial electron transport and ATP production. Dopamine *o*-quinone also forms adducts with and inactivates tyrosine hydroxylase, selenoprotein glutathione peroxidase 4, human dopamine transporter, and tryptophan hydroxylase (Xu et al., 1998; Whitehead et al., 2001; Kuhn & Arthur Jr, 1998; Hauser et al., 2013).

4.3 Aminochrome One-Electron Reduction

The aminochrome can be one-electron reduced to become a leukoaminochrome-*o*-semiquinone radical. This process is catalyzed by flavoenzymes that transfer electrons from NADH or NADPH to aminochrome. The leukoaminochrome-*o*-semiquinone radical is extremely reactive under aerobic conditions. It catalyzes the reduction of oxygen to superoxide and generates a redox cycle between the

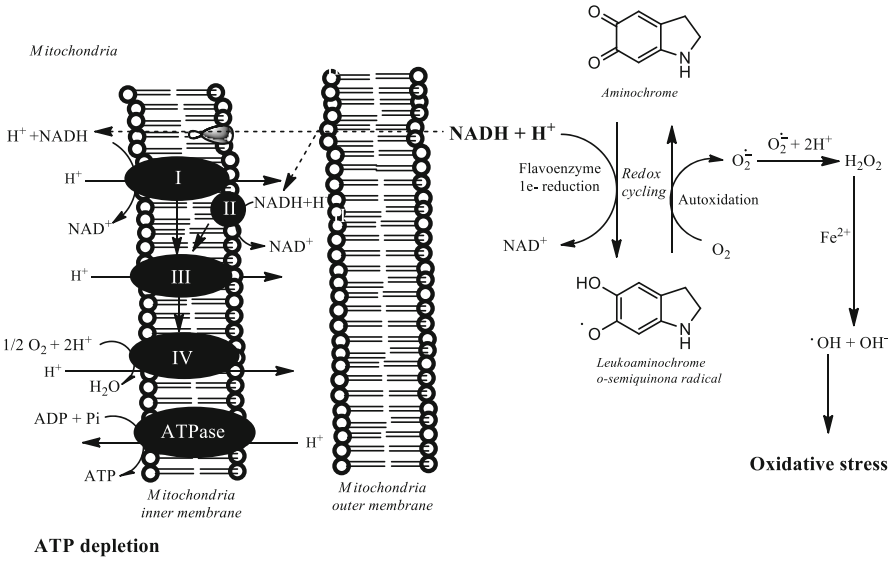

Fig. 7 One-electron reduction of aminochrome catalyzed by flavoenzymes that use NADH as electron donor

leukoaminochrome *o*-semiquinone radical and aminochrome (Baez et al., 1995; Segura-Aguilar et al., 1998).

The redox cycling between the leukoaminochrome *o*-semiquinone radical and aminochrome is important for aminochrome neurotoxicity. This process is catalyzed by flavoenzymes and transfers electrons from NADH or NADPH. NADH and oxygen depletion through redox cycling results in energy collapse because these molecules are no longer available for ATP synthesis in the mitochondria (Fig. 7). This effect is potentiated by the formation of superoxide radicals. These radicals spontaneously or enzymatically generate hydrogen peroxide, the precursor of hydroxyl radicals. NADPH can also be used as the electron donor in the reaction catalyzed by flavoenzymes. NADPH is involved in the reaction catalyzed by glutathione reductase that keeps GSH in the reduced state. As a result of NADPH depletion, GSH is unable to exert its antioxidant action, and oxidative stress is thereby increased. The one-electron reduction of aminochrome is neurotoxic in catecholaminergic cells (Paris et al. 2001, 2005, 2005, 2009, 2010, 2011; Arriagada et al., 2004; Fuentes et al., 2007; Díaz-Véliz et al., 2008; Muñoz et al. 2012, b, 2017; Herrera et al., 2017; Meléndez et al., 2019).

4.4 Aminochrome-Induced Adduct Formation

Aminochrome ability to form adducts with proteins and DNA is also a mechanism to induce neurotoxicity. It has been reported that aminochrome induces the formation

of adducts with alpha-synuclein (Muñoz et al., 2015), mitochondrial complex I (Aguirre et al., 2012), vacuolar H-type ATPase localized in lysosome membrane (Meléndez et al., 2019), actin, alpha- and beta-tubulin (Paris et al., 2010; Briceño et al., 2016). Dopamine *o*-quinone is the precursor of aminochrome and it is extremely unstable and at physiological pH it spontaneously cyclizes to aminochrome at the rate of 0.15 s^{-1} (Tse et al., 1976) and it has been reported to form adduct with large number of proteins including mitochondrial proteins, parkin, dopamine transporter, and tyrosine hydroxylase (Van Laar et al., 2009; LaVoie et al., 2005; Whitehead et al., 2001; Xu et al., 1998; Yu et al., 2015). However, the question is whether these adducts correspond to dopamine *o*-quinone or to aminochrome due to the high instability of dopamine *o*-quinone at physiological pH. In a study carried out with isolated mitochondria exposed to dopamine *o*-quinone in the test tube, where dopamine was oxidized by tyrosinase in the presence of isolated mitochondria, a long list of proteins that had adducts with dopamine *o*-quinone was observed. However, in the same study but now in a cell culture exposed to dopamine only, where dopamine oxidation occurred spontaneously in the cell cytosol, only a small amount of these proteins formed adducts with intracellularly oxidized dopamine (Van Laar et al., 2009). Aminochrome also induces damage to nuclear and mitochondrial DNA (Paris et al., 2011; Muñoz, et al., 2012).

4.5 Aminochrome Two-Electron Reduction

DT-diaphorase (NAD(P)H:quinone oxidoreductase1, NQO1) catalyzes the two-electron reduction of aminochrome (Segura-Aguilar & Lind, 1989), protecting dopaminergic neurons against aminochrome neurotoxicity (Herrera et al., 2017; Segura-Aguilar, 2021). This enzyme is unique among flavoenzymes because it catalyzes the two-electron reduction of quinones to hydroquinones preventing quinone one electron redox cycling. Other important function is its ability to keep reduced to ubiquinone and vitamin E. Since both NADH and NADPH can be used as electron donators in this reaction, the enzyme is also an efficient generator of NAD(P)+ (Ross & Siegel, 2017). More recently, news interest functions are emerging for NQO1 by modulating the microtubule acetylome (Siegel et al., 2021).

DT-diaphorase is a homodimeric flavoprotein with two sites actives. The catalysis in each of active sites occurs at different rates reflecting a negative cooperativity (Anoz-Carbonell et al., 2020). This mechanism of negative cooperativity binding is dependent on correct mobility of some key parts of the enzyme for its normal function (Pey et al., 2019). DT-diaphorase is mainly localized in the cytosol, but approximately 5% of this enzyme is associated with the mitochondria and endoplasmic reticulum. The enzyme has been also detected in nucleus mainly under conditions stress (Milković et al., 2019). It is found in different tissues and organs including the brain. The enzyme co-localizes with acetyl –tubulin and sirtuin 2 where its immunoreactivity is dependent of NAD(P)+/NAD(P)H redox environment altering its structure (Siegel et al., 2018). DT-diaphorase immunoreactivity also co-localizes with tyrosine hydroxylase-like immunoreactivity, suggesting that

DT-diaphorase is expressed in the dopaminergic neurons of both the substantia nigra and ventral tegmental area. The dense network of the DT-diaphorase-immunoreactive fibers in the striatum and the dopaminergic innervations were simultaneously lost following a 6-hydroxydopamine lesion. It is important to mention that DT-diaphorase constitutes 97% of the total cytosolic quinone reductase activity in the rat substantia nigra. DT-diaphorase immunoreactivity has also been found in Bergmann glia, astrocytes, and tanycytes (Schultzberg et al., 1988). DT-diaphorase catalyzes the reduction of aminochrome to leukoaminochrome (Segura-Aguilar & Lind, 1989). Leukoaminochrome autoxidizes in the presence of superoxide radicals (Fig. 8). However, the presence of superoxide dismutase in the cytosol prevents leukoaminochrome autoxidation (Baez et al., 1995). These in vitro results suggest that DT-diaphorase may protect against aminochrome neurotoxicity in neurons and astrocytes. Cell culture studies support this idea: DT-diaphorase inhibition with dicoumarol or siRNA induces aminochrome neurotoxicity (Arriagada et al., 2004; Lozano et al., 2010; Paris et al., 2011; Muñoz et al., 2012, 2015; Huenchuguala et al., 2016; Muñoz & Segura-Aguilar, 2017; Meléndez et al., 2019). DT-diaphorase also prevents the formation of alpha-synuclein oligomers and protofibrils (Segura-Aguilar et al., 2006; Cardenas et al., 2008; Muñoz et al., 2015); the cytoskeletal disruption arising from adduct formation with actin and α- and β-tubulin (Paris et al., 2010; Briceño et al., 2016); mitochondria dysfunction (Arriagada et al., 2004; Fuentes et al., 2007); proteasomal dysfunction (Zafar et al., 2006); oxidative stress (Arriagada et al., 2004; Paris et al., 2001). Recently, in vivo studies supported the neuroprotective role of DT-diaphorase suppressing toxicity of in vivo aminochrome (Herrera-Soto et al., 2017).

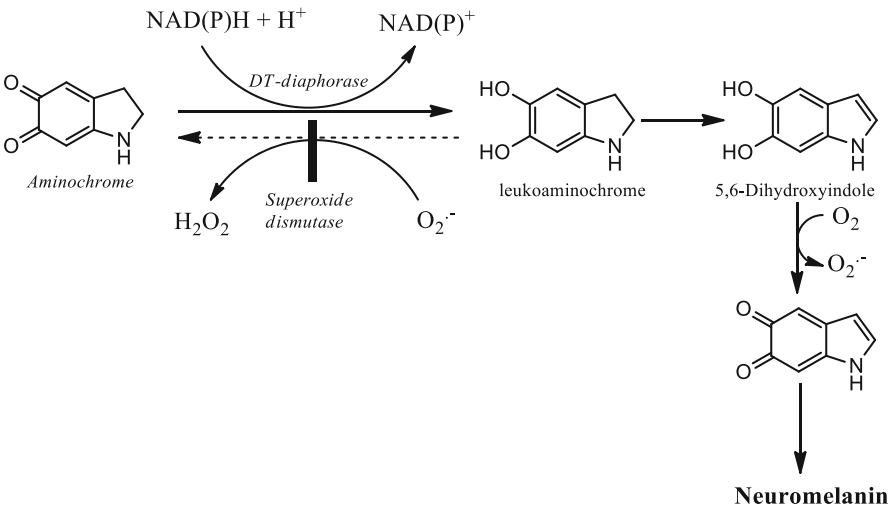

Fig. 8 DT-diaphorase catalyzes the two-electron reduction of aminochrome

4.6 Aminochrome Conjugation with Glutathione

The glutathione transferases M2-2 (GSTM2; EC 2.5.1.18) belong to class mu isoenzyme of glutathione S-transferases. This enzyme catalyzes the reaction of conjugation of glutathione to wide variety of organic compounds. GSTM2 is present in brain and has a key role in detoxification of aminochrome and dopamine *o*-quinone. Thus, aminochrome can be conjugated with glutathione by the enzyme GSTM2 to 4-*S*-glutathionyl-5,6-dihydroxyindoline (Fig. 9). The 4-*S*-glutathionyl-5,6-dihydroxyindoline molecule is stable in the presence of biological oxidizing agents such as oxygen, superoxide radicals, and hydrogen peroxide (Segura-Aguilar et al., 1997; Baez et al., 1997). This stability suggests that the molecule is a final elimination product. Interestingly, the precursor of aminochrome dopamine *o*-quinone is also conjugated by GSTM2 to 5-glutathionyl-dopamine (Fig. 9). This process prevents the formation of aminochrome (Dagnino-Subiabre et al., 2000). The tripeptide γ-L-Glu-L-Cys-Gly of all glutathione conjugates undergoes glutathione degradation to cysteine conjugation. Therefore, 5-*S*-glutathionyl-dopamine is ultimately converted to 5-*S*-cysteinyl dopamine (Shen et al., 1996). Interestingly, 5-*S*-cysteinyl-dopamine has been detected in the cerebrospinal fluid of Parkinson's disease patients and in dopamine-rich brain regions such as the caudate nucleus,

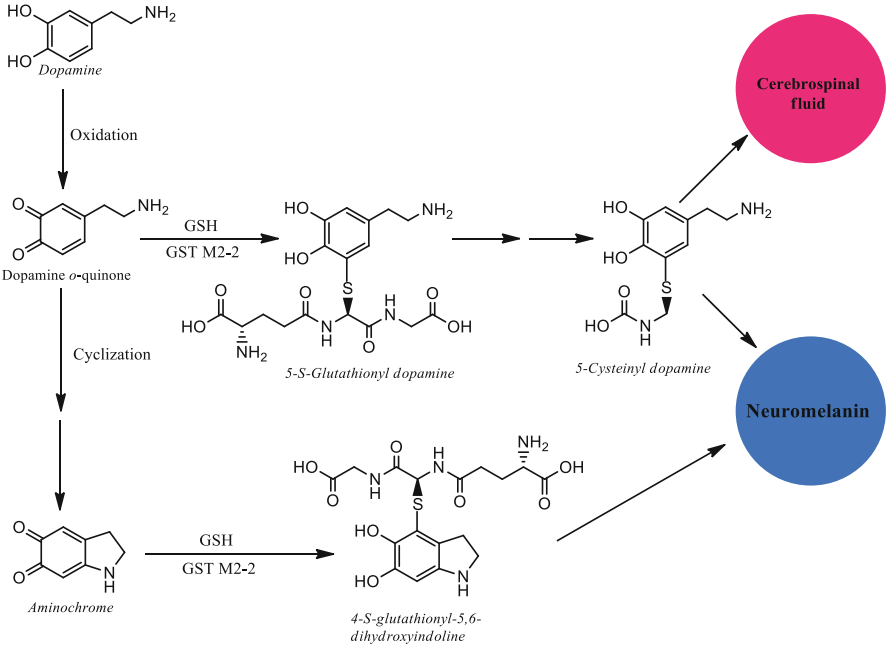

Fig. 9 Glutathione (GSH) conjugation of aminochrome and dopamine *o*-quinone catalyzed by glutathione S-transferase M2-2 (GST M2-2)

putamen, globus pallidus, and substantia nigra as well as in neuromelanin (Cheng et al., 1996; Rosengren et al., 1985; Carstam et al., 1991). Similarly, higher 5-*S*-cysteinyl-dopamine levels compared to DOPAC levels were detected in cerebrospinal fluid of patients with Parkinson's disease. Specifically, 5-*S*-cysteinyl-dopamine/DOPAC ratios were significantly increased in these patients (Goldstein et al., 2016). GSTM2 also catalyzes the conjugation of dopa *o*-quinone to 5-*S*-glutathionyl dopa. The tripeptide glutathione on 5-*S*-glutathionyl dopa undergoes degradation to generate 5-cysteinyl dopa (Dagnino-Subiabre et al., 2000). Melanoma cells produce and release 5-cysteinyl-dopa, which is ultimately excreted through urine (Ito et al., 1984). The 5-S-cysteinyl-dopa has been also detected in the serum of patients with advanced stage malignant melanoma. Their levels in serum have great usefulness to be used as a biomarker for predicting prognosis, detecting relapse, and evaluating the efficacy of a treatment (Umemura et al., 2017, 2019).

Currently, various evidences indicate that the conjugation of glutathione must be protective against aminochrome neurotoxicity. Aminochrome induces microglia and astrocyte activation and neuronal death in primary culture derived from rats (Santos et al., 2017). Similarly, aminochrome induces neuroinflammation, as well as negative regulation of neurotrophic factors (GDNF and NGF) in organotypic midbrain slice cultures (de Araújo et al., 2018). GSTM2 prevents aminochrome-induced cell death, autophagy-lysosome and mitochondrial dysfunction in glioblastoma cells (Huenchuguala et al., 2014, 2017). Aminochrome-glutathione conjugate formed by GSTM2 participates in the formation of apparently no toxic aminochrome-glutathione alpha-synuclein oligomers (Huenchuguala et al., 2019).

Glutathione transferase is expressed in human astrocytes that are exposed to extracellular dopamine released during neurotransmission. Astrocytes express transporter that takes up dopamine. In the cytosol of astrocytes dopamine can be autoxidized to form dopamine *o*-quinone and aminochrome that are conjugated with glutathione in a reaction catalyzed by GSTM2. However, it has been observed that the formation of aminochrome within astrocytes increases the expression of GSTM2 and it has been observed that astrocytes secrete glutathione transferase into the extracellular space. Interestingly, dopaminergic neurons uptake GSTM2 and protect astrocytes from the toxic effects of aminochrome. Cell traffic between astrocytes and dopaminergic neurons is mediated by exosomes loaded with glutathione transferase. This demonstrates the protective role of astrocytes against the neurotoxic effects of aminochrome on dopaminergic neurons (Cuevas et al., 2015; Segura-Aguilar, 2015, 2017a, b; Valdes et al., 2021; Segura-Aguilar et al., 2021).

4.7 Neuroprotection Against Aminochrome-Induced Neurotoxicity

Aminochrome is a neurotoxin that is formed during the oxidation of dopamine to ortho-quinones in the synthesis of neuromelanin that accumulates with age in human dopaminergic neurons (Zecca et al., 2002; Xing et al., 2018). However, neuromelanin-containing dopaminergic neurons located in the substantia nigra of

healthy elderly brains are intact even though dopamine was oxidized to neuromelanin through the formation of aminochrome. This apparent contradiction can be explained by the existence of two enzymes that prevent the neurotoxic effects of aminochrome in dopaminergic neurons. DT-diaphorase reduces aminochrome with two electrons to leukoaminochrome and prevents aminochrome-induced neurotoxicity, mitochondrial dysfunction, protein degradation dysfunction of both lysosomal and proteasomal systems, alpha-synuclein aggregation to neurotoxic oligomers, lysosome dysfunction, oxidative stress, neuroinflammation, and disruption of the cytoskeleton (Muñoz et al., 2015; Zafar et al., 2006; Arriagada et al., 2004; Fuentes et al., 2007; Lozano et al., 2010; Paris et al., 2010; Segura-Aguilar et al., 2014; Meléndez et al., 2019; Herrera et al., 2016, 2017; Herrera-Soto et al., 2017). DT-diaphorase is expressed both in dopaminergic neurons and astrocytes (Schultzberg et al., 1988). DT-diaphorase also protects astrocytes against aminochrome toxicity (Huenchuguala et al., 2016). Glutathione transferase M2-2 catalyzes aminochrome and its precursor dopamine *o*-quinone conjugation with glutathione (Segura-Aguilar et al., 1997; Baez et al., 1997; Dagnino-Subiabre et al., 2000), preventing the neurotoxic effects of aminochrome such as neurotoxicity, mitochondrial dysfunction, autophagy dysfunction, alpha-synuclein aggregation to neurotoxic oligomers, and lysosome dysfunction (Huenchuguala et al., 2014, 2017, 2019; Segura-Aguilar & Huenchuguala, 2018). Human glutathione transferase M2-2 is expressed in astrocytes that express transporters that take up dopamine and prevent toxic effects generated by the oxidation of dopamine within astrocytes. However, it has been shown that GSTM2 also protects dopaminergic neurons since astrocytes secrete this enzyme through exosomes that explain the uptake of this enzyme in dopaminergic neurons and its neuroprotective effect on these neurons (Cuevas et al., 2015; Segura-Aguilar, 2015, 2017a, b; Valdes et al., 2021) (Fig. 10).

5 Aminochrome and Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of cytoplasmic inclusions containing mainly the protein alpha synuclein, called Lewy bodies. Parkinson's disease is a multisystem disorder where several regions of the brain seem to be affected by altering not only the dopaminergic system (Miguelez et al., 2020). Although it is classified as a movement disorder, nonmotor symptoms can occur years before onset of the disease in premotor phases (Goldman & Postuma, 2014; Kaiserova et al., 2021). The discovery that Parkinson's disease patients show a loss of neuromelanin-containing dopaminergic neurons led to intensive research focused on understanding the mechanisms involved in the loss of dopaminergic neurons, which results in motor symptoms. Recently, the presymptomatic and symptomatic phases of Parkinson's disease were subdivided into six stages (Braak et al., 2004). The progressive loss of nigral neurons with Lewy bodies is considered to be an essential neuropathological feature. However, olfactory disturbances, sleep fragmentation, gastrointestinal dysfunction, and depression precede the motor

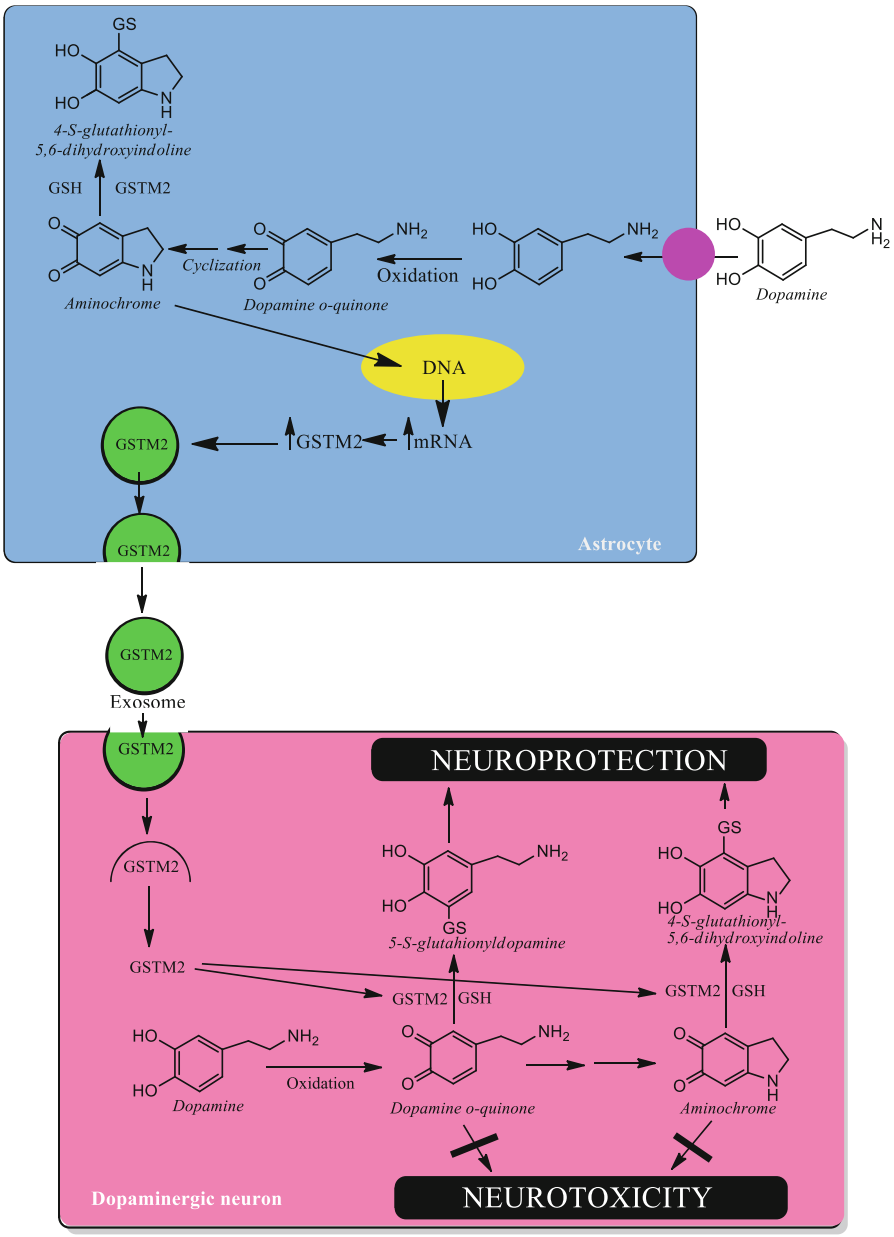

Fig. 10 Neuroprotective effect of GSTM2 against aminochrome-induced toxicity in neuronal and astrocytes cells

symptoms (Wolters & Braak, 2006; Cersosimo et al., 2013; Goldman & Postuma, 2014; Kaiserova et al., 2021). The disease may initially affect the olfactory bulb, enteric plexus, and motor component of cranial nerve X (stage 1). It may progress to

the locus coeruleus, caudal raphe, and magnocellular reticular formation (stage 2). Approximately 5 years before the manifestation of the motor symptoms, the substantia nigra, amygdala central subnucleus, Meynert's nucleus, and pedunculopontine tegmental nucleus are affected (stage 3). Approximately 4 years after the manifestation of motor symptoms, the transentorhinal cortex, CA2 plexus, and intralaminar thalamic nuclei are affected (stage 4). Approximately 10 years after the manifestation of motor symptoms, the prefrontal cortex and tertiary sensory association areas are affected (stage 5). Finally, the secondary and then the primary motor and sensory areas are affected (stage 6) (Hawkes et al., 2010).

Despite the therapeutic efficacy of L-dopa for Parkinson's disease, the role of substantia nigral neurodegeneration (stage 3) in the motor symptoms of the disease remains unclear. The association of the alpha-synuclein (Polymeropoulos et al., 1997) and parkin (Hattori et al., 1998; Abbas et al., 1999) genes with the familial form of Parkinson's disease was important in understanding possible mechanisms underlying the sporadic form of the disease. A recent study large-scale genome-wide association detected over 40 loci that increase risk of Parkinson's disease. Overlapping between familial and sporadic Parkinson's disease genes, specifically for SNCA and LRRK2 genes-containing loci were identified. Findings suggest that both Parkinson's disease forms could share pathogenic mechanisms (Reed et al., 2019). Several other genes have also been linked with familial Parkinson's disease and common genetic variability at 90 loci have been associated to risk for Parkinson's disease (for review see Bandres-Ciga et al., 2020). Despite the enormous advances in the field, the neurotoxins and mechanisms involved in Parkinson's disease-related neurodegeneration remain unclear. However, the mechanisms of dopaminergic neurodegeneration are generally thought to involve mitochondrial dysfunction, the formation of neurotoxic oligomers of alpha-synuclein, protein degradation dysfunction, oxidative and endoplasmic reticulum stress, and neuroinflammation (Schapira, 2011; Conway et al., 2001; McNaught et al., 2004; Cuervo et al., 2010; Schapira & Jenner, 2011; Ge et al., 2020; Lu et al., 2020; Du et al., 2020; Pajares et al., 2020).

The proposed timeline for Parkinson's disease (Hawkes et al., 2010) suggests that approximately 5 years elapse between the stage 3 damage to the substantia nigra and the appearance of motor symptoms (stage I in the Hoehn & Yahr scale). The progression of the disease after the manifestation of the motor symptoms is also very slow. It takes approximately 10 years to progress to stage III of the Hoehn & Yahr scale. These data refute the possibility that an exogenous neurotoxin is involved in the idiopathic degeneration of the dopaminergic neurons in the substantia nigra. This possibility is unlikely because MPTP induced severe Parkinsonian motor symptoms in 3 days (Williams, 1984). It is also important to note that the neuromelanin-containing dopaminergic neurons in the substantia nigra are lost, suggesting that the dopamine in the degenerative cells oxidizes to aminochrome, the precursor of neuromelanin.

Several candidates at endogenous neurotoxins have been postulated, among them, alpha-synuclein neurotoxic oligomers, 4-dihydroxyphenylacetaldehyde, and ortho-quinones generated during dopamine oxidation pathway toward neuromelanin (Segura-Aguilar & Kostrzewa, 2015; Segura-Aguilar et al., 2016; Segura-Aguilar,

2017b, 2018). It was proposed that aminochrome is the endogenous neurotoxin involved in the neurodegeneration of the neuromelanin-containing dopaminergic neurons in Parkinson's disease. This compound could induce focal neurotoxic events in the years prior to the development of motor symptoms. The following evidence supports this idea: (i) aminochrome induces mitochondrial dysfunction by forming adducts with complexes I in the electron transport chain (Arriagada et al., 2004; Aguirre et al., 2012; Yu et al., 2015; Herrera et al., 2016; Huenchuguala et al., 2017; Segura-Aguilar & Huenchuguala, 2018; Segura-Aguilar, 2019). The redox cycling induced by aminochrome one-electron reduction depletes NADH, thereby decreasing ATP production in cell culture (Muñoz et al., 2012; Huenchuguala et al., 2017); (ii) aminochrome induces the formation of neurotoxic alpha-synuclein oligomers (Muñoz et al., 2015); (iii) aminochrome induces protein degradation dysfunction of both lysosomal and proteasomal systems (Zafar et al., 2006; Muñoz et al., 2012; Huenchuguala et al., 2014, 2017; Meléndez et al., 2019; Segura-Aguilar & Huenchuguala, 2018); (iv) aminochrome induces neuroinflammation (de Araújo et al., 2018; Santos et al., 2017); (v) aminochrome induces oxidative stress (Arriagada et al., 2004; Paris et al., 2001); (vi) aminochrome induces endoplasmic reticulum stress (Xiong et al., 2014); (vii) aminochrome also induces the aggregation of α- and β-tubulin through forming adducts with these proteins and disrupting cytoskeleton architecture (Paris et al., 2010). Aminochrome inhibits the microtubule formation (Briceño et al., 2016) required for the fusion of antiphagocytic vacuoles and lysosomes (Monastyrska et al., 2009). The latter may contribute to autophagy-lysosomal dysfunction induced by aminochrome (Meléndez et al., 2019; Muñoz & Segura-Aguilar, 2017; Segura-Aguilar & Huenchuguala, 2018). (viii) Finally, aminochrome induces neuroinflammation by activating microglia and astrocyte (Santos et al., 2017; de Araújo et al., 2018). Interestingly, aminochrome may play a role in all mechanisms that are generally accepted as being involved in the degeneration of neuromelanin-containing dopaminergic neurons in Parkinson disease. Remarkably, DT-diaphorase and GSTM2 are considered as the most important neuroprotective mechanisms to prevent neurotoxic mechanism induced by aminochrome (Muñoz et al., 2015; Cuevas et al., 2015; Huenchuguala et al., 2014, 2016, 2017; Valdes et al., 2021).

6 Conclusion

Despite the fact that more than 200 years have passed since Parkinson's disease was described, its etiology remains unknown. Currently there is no cure and treatments are only palliative without stopping the progress of this disease. Several exogenous toxins are used as models to study the disease; however, these do not explain the slow progress that characterizes this disorder. Thus, the existence of an endogenous neurotoxin is gaining greater acceptance. It was proposed that aminochrome is the endogenous neurotoxin involved in the neurodegeneration of the neuromelanin-containing dopaminergic neurons in Parkinson's disease. This compound could induce focal neurotoxic events in the years prior to the development of motor symptoms. Aminochrome has

been shown to be toxic in both in vitro and in vivo models. To prevent aminochrome formation and its toxic effects, dopamine neurons uptake dopamine into the monoaminergic synaptic vesicles by vesicular monoaminergic transporter-2 (VMAT-2). However, under certain unknown conditions dopamine oxidize to aminochrome, the precursor of neuromelanin, which is a pigment localized in substantia nigra and is present in normal subjects. Aminochrome could induce toxicity through (i) the one-electron reduction of aminochrome by forming leukoaminochrome-*o*-semiquinone radical, molecule extremely reactive with oxygen that autoxidizes depleting both NADH and O_2 required for ATP synthesis; and (ii) by forming adducts with proteins such as alpha synuclein, mitochondrial complex I of electron transport chain, vacuolar H-type ATPase and actin, and α- and β-tubulin. In consequence, aminochrome may induce the focal neurodegeneration of dopaminergic neurons through mechanisms involving protein aggregation, protein degradation dysfunction, mitochondrial dysfunction, cytoskeleton dysfunction, oxidative stress, neuroinflammation, and endoplasmic reticulum stress. Interestingly, aminochrome may play a role in all mechanisms that are generally accepted as being involved in the degeneration of neuromelanin-containing dopaminergic neurons in Parkinson disease. Remarkably, DT-diaphorase and GSTM2 are considered as the most important neuroprotective mechanisms to prevent neurotoxic mechanism induced by aminochrome. The discovery of molecular biomarkers that together with the symptoms allow the early diagnosis of this disease, the design of new therapies that aim not only to treat the symptoms but also to slow the progression of this disease will be real challenges for the scientific community. However, this will be impossible if the model used is wrong.

7 Cross-References

- ► Alpha-Synuclein Toxicity: An Insight on Controversial Issues
- ► Autophagy and Parkinson's Disease
- ► Dopamine Homeostasis and Role of VMAT2 in Neurodegeneration
- ► Iron Neurotoxicity in Parkinson's Disease
- ► Iron-Induced Dopaminergic Cell Death In Vivo as a Model of Parkinson's Disease
- ► Manganese Neurotoxicity
- ► Neuromelanin and Parkinson's Disease
- ► Neuroprotection and Neurorestoration of Nigra Striatal Dopamine Neurons by Novel Multitarget Drugs, M30

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