Chapter 2
Dopamine Metabolism and Reactive Oxygen Species Production

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Abbreviations

AADC	Aromatic amino acid decarboxylase
ALDH	Aldehyde dehydrogenase
ANLSH	Astrocyte–neuron lactate shuttle hypothesis
ApN	Aminopeptidase N
BBB	Blood–brain barrier
BH4	Tetrahydrobiopterin
CA	Catecholamine
COMT	Catechol-*O*-methyltransferase
DA	Dopamine
DAB	Dopamine-beta-hydroxylase
DAT	Dopamine transporter
DHPR	Dihydropteridine reductase
DOPAC	3,4-Dihydroxyphenylacetic acid
DOPAL	3,4-Dihydroxyphenylaldehyde
DOPET	3,4-Dihydroxyphenylethanol
DT Diaphorase	NAD(P)H:quinone oxidoreductase
E	Epinephrine
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Reduced glutathione
GSSG	Oxidized glutathione

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L.M. Buhlman (ed.), *Mitochondrial Mechanisms of Degeneration and Repair in Parkinson's Disease*, DOI 10.1007/978-3-319-42139-1_2

HVA	Homovanillic acid
L-DOPA	L-3,4-Dihydroxyphenylalanine
MAO	Monoamine oxidase
MCT	Monocarboxylate transporter
NE	Norepinephrine
NM	Neuromelanin
NO	Nitric oxide
NOS	Nitric oxide synthase
PD	Parkinson's disease
PNMT	Phenylethanolamine-*N*-methyltransferase
PST	Phenylsulfotransferase
PTP	Permeability transition pore
ROS	Reactive oxygen species
SN	Substantia nigra
SOD	Superoxide dismutase
TCA	Tricarboxylic acid
TH	Tyrosine hydroxylase
UGT	Uridine diphosphoglucuronosyltransferases
VMAT2	Vesicular monoamine transporter 2
γ-GT	Gamma-glutamyl transpeptidase

2.1 Dopamine Metabolism

2.1.1 Dopamine Biosynthesis

Dopamine (DA) is a hormone and neurotransmitter and belongs to the group of catecholamines (CAs). It can be found in both the central and the peripheral nervous system. After its discovery at the beginning of the twentieth century, DA was primarily believed to be the precursor of norepinephrine. It was not until 1959 that Carlsson suggested a more important role for DA itself after finding that the distribution pattern of DA in the brain is different from that of norepinephrine [1]. Based on current knowledge, DA can be synthesized by cells via three different pathways (Fig. 2.1). The first and main pathway, which is carried out in neuronal cells in vivo, was first described in 1939 and starts from the amino acid tyrosine [2]. In a first step, L-3,4-dihydroxyphenylalanine (L-DOPA) is produced by hydroxylation of tyrosine at the *ortho*-position of the phenol ring. This reaction is catalyzed by the enzyme tyrosine hydroxylase (TH) that belongs to the family of biopterin-dependent aromatic amino acid hydroxylases. During the second step, L-DOPA is decarboxylated by the enzyme aromatic amino acid decarboxylase (AADC) to form DA. The hydroxylation by TH represents the regulatory switch of DA-synthesis: (1) TH activity is dependent on the availability of its cofactor tetrahydrobiopterin (BH_4), and (2) TH is strongly regulated on both the transcriptional and posttranscriptional level, including allosteric control, covalent modifications, and protein–protein interactions [3]. A second option to produce DA is given through the activity of the

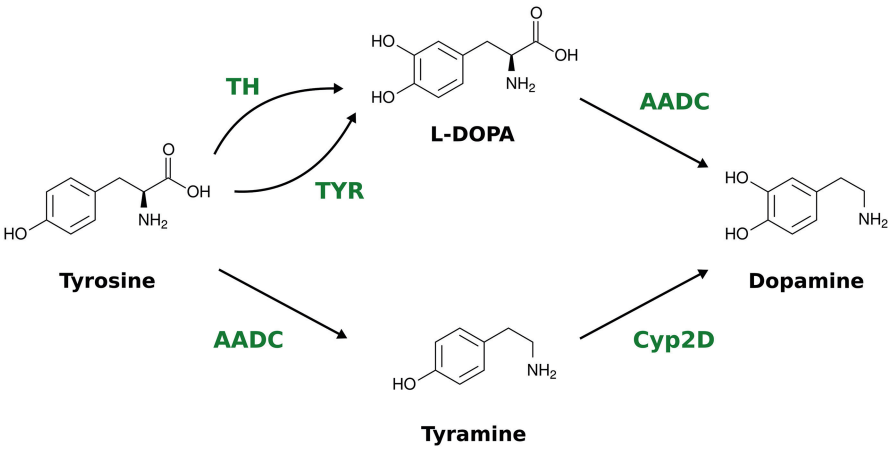


Fig. 2.1 Dopamine synthesis. DA can be synthesized via three different pathways. The classical pathway consists of hydroxylation of tyrosine by TH followed by AADC-catalyzed decarboxylation. Under TH-deficient conditions, TYR has been shown to produce L-DOPA instead of dopaquinone in order to ensure sufficient DA production. In a third pathway, tyrosine is first decarboxylated to form tyramine which is subsequently hydroxylated by the P450 enzyme Cyp2D

metalloenzyme tyrosinase. Like TH, this enzyme catalyzes the hydroxylation of tyrosine to L-DOPA, but in a second reaction further oxidizes L-DOPA to form dopaquinone. In melanocytes (pigment-producing cells present in the skin), dopaquinone is used as a precursor to form the black polymer–pigment eumelanin [4–6]. However, it has also been shown that tyrosinase activity can lead to DA production in TH-deficient mice [7]. In this case the reaction stops at L-DOPA, which is subsequently decarboxylated to DA. A third DA-producing pathway was identified in rats in vivo [8]. For this pathway, the series of reactions is reversed compared to the other two pathways: tyrosine is first decarboxylated by AADC to yield tyramine and then hydroxylated by Cyp2D enzymes belonging to the cytochrome-P450 family to form DA.

2.1.2 Dopamine Degradation

The controlled and enzymatically catalyzed degradation of cytoplasmic DA represents a crucial part of its metabolism in the brain (Fig. 2.2). If DA is not actively degraded by the cell, it easily auto-oxidizes, leading to the formation of highly reactive intermediates as well as reactive oxygen species (ROS). DA degradation is carried out both in glial cells and DAergic neurons. Glial cells take up DA released by neurons into the synaptic cleft during signal transmission, but transporter-mediated DA reuptake is also observed in neurons [9]. There, it is recycled by being repackaged into synaptic vesicles via the vesicular monoamine transporter 2

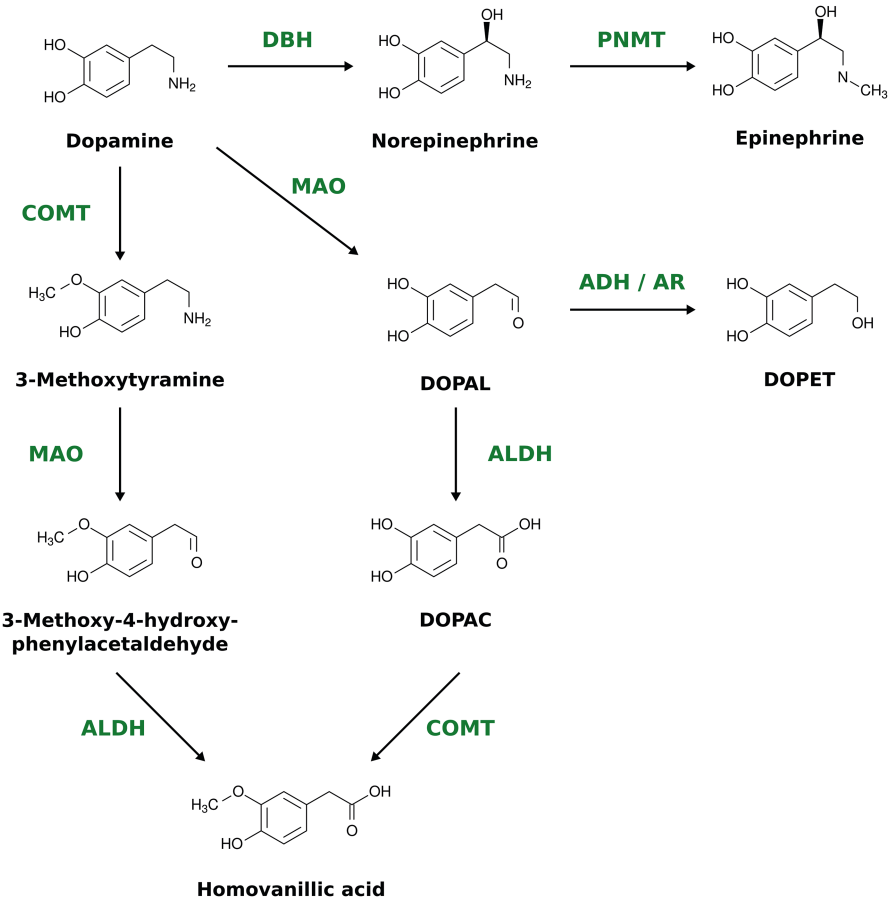


Fig. 2.2 Enzymatic dopamine degradation. DA can be hydroxylated to form the neurotransmitter norepinephrine. Further methylation at the amino group results in epinephrine. The DA degradation product homovanillic acid can be produced by two pathways, both using the enzymes MAO, ALDH, and COMT in different order. DOPET is derived from the degradation intermediate DOPAL via ADH- or AR-catalyzed reduction of the aldehyde moiety

(VMAT2). In neurons, DA degradation only takes place when DA leaks into the cytosol. Both cell types are able to oxidize DA via the mitochondria-associated enzyme monoamine oxidase (MAO) to form 3,4-dihydroxyphenylacetaldehyde (DOPAL). Hydrogen peroxide is formed as a by-product of this reaction. DOPAL can afterwards either be oxidized to its corresponding acid (3,4-dihydroxyphenylacetic acid, DOPAC) or reduced to the corresponding alcohol (3,4-dihydroxyphenylethanol, DOPET). DOPAC can undergo a further methylation step of the 3′-hydroxyl group of the catechol ring, resulting in homovanillic acid (HVA). This step is catalyzed by the catechol-*O*-methyltransferase (COMT). COMT can also first act on DA to form 3-methoxytyramine, which is then oxidized by MAO. The resulting intermediate

3-methoxy-4-hydroxyphenylacetaldehyde is subsequently oxidized to HVA by aldehyde dehydrogenase (ALDH). In addition to its own role as a neurotransmitter, DA is also the direct precursor of norepinephrine, which is formed by the DA-β-hydroxylase (DAB) reaction. Subsequently, norepinephrine can be methylated at the amino group to form epinephrine. This reversible reaction is carried out by the enzyme phenylethanolamine-*N*-methyltransferase (PNMT).

Besides these processes, which are mainly based on oxidation and reduction, there is also the possibility of DA degradation by sulfate and glucuronide conjugation. Such processes are referred to as *phase II* reactions and are often performed by hepatic and renal enzymes, but can also be found in the central nervous system [10]. The aim of these reactions is to covalently attach polar groups to target molecules and increase their water solubility. The modified molecules can then easily be eliminated via the renal system. Sulfurylation and glucuronidation are not only performed on DA itself but also on its degradation products [11]. The responsible enzymes for this mechanism are phenylsulfotransferases (PSTs) and uridine diphosphoglucuronosyltransferases (UGTs), which transfer the respective groups from either 3′-phosphoadenosine-5′-phosphosulfate or UDP glucuronic acid to the target molecule. Conjugation always takes place at one of the hydroxyl groups of the catechol moiety, resulting in a mix of 3- and 4-sulfates and glucuronides [12, 13]. The extent to which either of these reactions is performed strongly differs between species and even tissues.

2.2 The Role of Neuromelanin in Dopaminergic Neurons

Under physiological conditions, intracellular dopamine (DA) is prone to spontaneous and iron-catalyzed oxidation [14]. The oxidation products emerging from this process are highly reactive and can produce ROS which in turn cause elevated oxidative stress levels to DA-producing cells. There are several mechanisms available to a cell to prevent the accumulation of excessive amounts of DA: (1) transport of DA into synaptic vesicles and their subsequent secretion [15], (2) enzymatic degradation of DA [3], and (3) polymerization of DA and its metabolites to form neuromelanin (NM) [16].

Since the first two of these processes are associated with strongly regulated physiological functions of DAergic cells, their ability to decrease cytoplasmic DA levels is limited. The lesser regulated polymerization of DA and its oxidation products to form NM however seems to represent a more effective sink for these highly reactive compounds. NM is a polymer pigment mostly found in catecholaminergic neurons of the substantia nigra (SN) and the locus coeruleus of the human brain [17–19], but was also shown to be present in other brain areas in lower amounts [20–24]. NM consists of a melanic structure with proteins and lipids covalently attached to it (Fig. 2.3). Comparison with synthetic melanins has suggested that the melanic part of NM is a mixed-type pigment comprising both eu- and pheomelanin [25]. The eumelanin part mainly consists of polymerized oxidation products of DA and

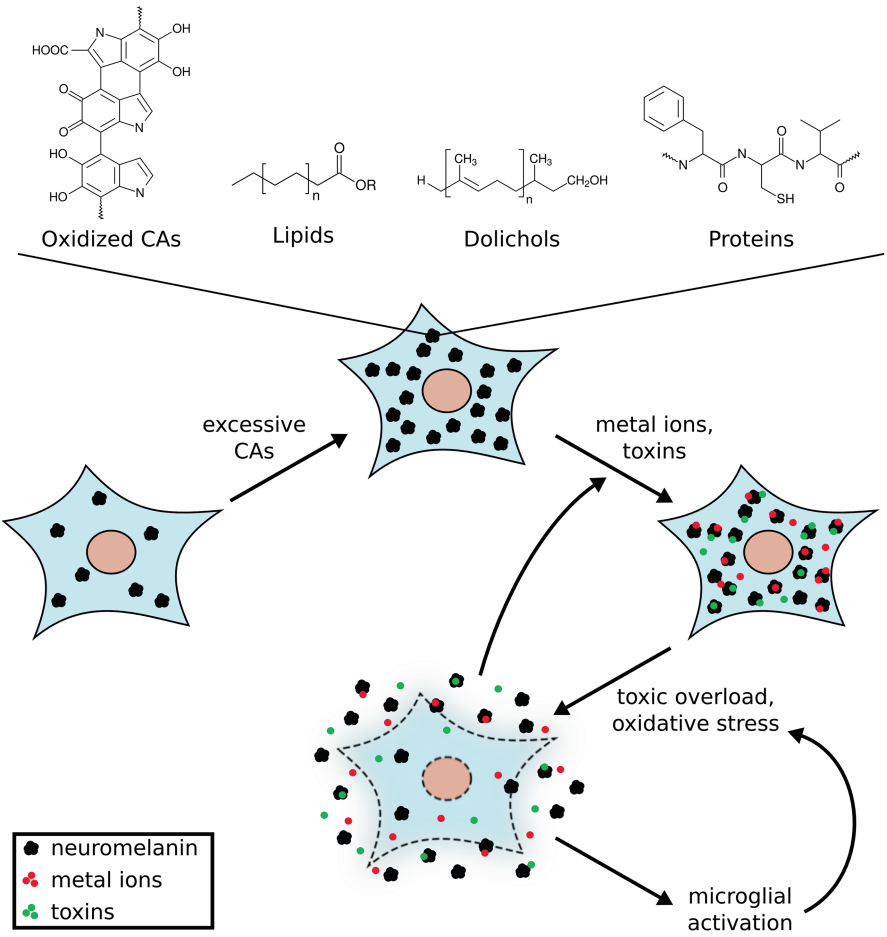


Fig. 2.3 NM biosynthesis in SN neurons is triggered by excessive cytoplasmic levels of CAs. NM can bind substantial amounts of metal ions (mostly iron) and organic toxins to prevent cell damage. These molecules are released upon cell death and can cause damage to surrounding cells. NM release further induces an inflammatory response by microglial activation which leads to oxidative stress

L-DOPA, namely, 5,6-dihydroxyindole and 5,6-dihydroxyindole-2-carboxylic acid [26]. For the pheomelanin part, oxidized cysteine is additionally integrated into the polymer. Studies investigating the composition and macromolecular structure of NM have found that lipids (mainly dolichols) account for around 18 % of pigment mass, while another 12–15 % are composed of peptides [27]. NM granules undergo autophagy and are enclosed by a lipid bilayer. The produced organelles can later fuse with lysosomes during their maturation process.

The synthesis process of NM has not yet been completely elucidated; however, several findings point toward a mostly auto-oxidative buildup of the pigment.

The metalloenzyme tyrosinase plays a vital role during the synthesis of peripheral melanins [4–6], but NM levels in tyrosinase-deficient albinos remain unchanged [18], thus suggesting a tyrosinase-independent synthesis process. In addition, no other enzymes are known to play a role during NM synthesis. Sulzer and colleagues have shown that treatment of PC-12 cells with the dopamine precursor L-DOPA leads to an increased production of NM granules [28]. Overexpression of the synaptic vesicle CA transporter VMAT2 inhibited NM biosynthesis by decreasing cytosolic DA levels. These results show that NM synthesis strongly depends on the cystolic availability of DA. By removing excessive amounts of potentially harmful CA intermediates from the cytosol, NM might thus exert a neuroprotective function.

Besides its ability to trap CAs, NM is also able to bind large quantities of iron and other metal ions (e.g., copper, zinc, and lead) as well as neuronal toxins (e.g., paraquat and MPP^+) [29–32]. This does not only play a pivotal role in iron homeostasis but also in the prevention of iron-catalyzed oxidation of CAs and metal ion- or toxin-mediated neurotoxicity. The iron contained in NM is mostly in the ferric state (Fe^{3+}) and can be bound to the melanic portion at two sites, differing in their binding strength [33, 34]. Under normal conditions, most of the iron is tightly bound to high affinity sites. In these sites, the iron is coordinated by catechol groups and remains in an inactive form, thus preventing oxidative reactions. When an excess of iron is present in the cytosol, as reported during Parkinson's disease (PD) [35, 36], most of these sites are occupied. Iron is then also bound to low affinity sites. As the binding to these sites is not as effective as to high affinity sites, the iron remains redox-active, thus promoting oxidative reactions.

Following neuronal cell death, NM is released into the extracellular space, where it can trigger a series of detrimental events. Released NM has been shown to induce an immune response by microglial activation in PD patients [37–39]. As a part of this process, several pro-inflammatory proteins and molecules such as tumor necrosis factor alpha, interleukin-6, and nitric oxide are released from the microglial cells [40]. The initial response is readily turned into a chronic inflammatory process [41]. This might be explained by the fact that NM is not soluble and, due to its complex composition, only slowly degraded. The high density of microglial cells in the SN additionally increases the intensity of this response [42]. Metal ions and toxins which were previously bound to the pigment can be released into the extracellular space. This in turn represents another source for ROS production, eventually leading to the death of more neurons and glial cells. The result of this series of processes is a vicious cycle where oxidative stress leads to neuronal cell death and vice versa (Fig. 2.3). It is conceivable that this series of events is one of the factors which are driving the progression of PD in vivo.

In summary, NM can play two opposing roles, depending on the cellular context [43]. Under normal conditions, NM is able to serve as a sink for excessive amounts of CAs, which helps in preventing the accumulation of ROS. It also plays a vital role in iron homeostasis and can bind other metal ions and organic compounds, thus decreasing their toxicity. This beneficial role is however easily reversed under stressed conditions as occurring during PD. Iron overload leads to its binding to low

affinity sites, where it remains redox-active. NM released from dead cells is only slowly degraded and induces an immune response by microglial activation. When present in the extracellular space, NM releases previously bound metals and toxins, which represent an additional burden to the already stressed cells.

2.3 ROS Production During Dopamine Metabolism

ROS are produced during the metabolism of DA either enzymatically or nonenzymatically. In the first case, the most important enzyme involved in ROS production is MAO. This process is believed to occur under low concentrations of intracellular DA. With increasing intracellular DA concentrations, an increase in ROS production caused by the autoxidation of degradation products results in an inhibition of mitochondrial respiration [44].

2.3.1 MAO-Linked ROS Production

MAO is located in the outer membrane of mitochondria [45] and catalyzes the degradation of DA to DOPAL (Fig. 2.4) via the following reaction (2.1):

$$\mathrm{DA} + \mathrm{O_2} + \mathrm{H_2O} \rightarrow \mathrm{DOPAL} + \mathrm{H_2O_2} + \mathrm{NH_3}. \tag{2.1}$$

DOPAL has been shown to induce mitochondrial permeability transition pore (PTP) opening, which can trigger cell death [46]. PTP opening will be discussed in more detail later on.

Hydrogen peroxide (H_2O_2) is a natural by-product of respiration, and about 1–3 % of the O_2 consumed by a cell is converted to H_2O_2 [47]. However, during MAO activity, the amount of H_2O_2 produced can increase 100-fold [48]. Due to the iron-rich environment in the substantia nigra pars compacta [49], H_2O_2 can react with iron via the Fenton reaction and generate hydroxyl radicals, which are highly reactive and damaging, causing DNA mutations, lipid peroxidation, and modification of certain amino acids [50].

Thus, given the risks generated by high concentration of H_2O_2, it has to be detoxified. Because mitochondria do not contain the catalase enzyme [45], the enzyme catalyzing this reaction is glutathione peroxidase (GPx). This enzyme is located in the mitochondrial matrix and at the contact points between the inner and outer mitochondrial membrane [51]. It catalyzes the following reaction (2.2):

$$\mathrm{H_2O_2} + 2\mathrm{GSH} \rightarrow \mathrm{GSSG} + 2\mathrm{H_2O}. \tag{2.2}$$

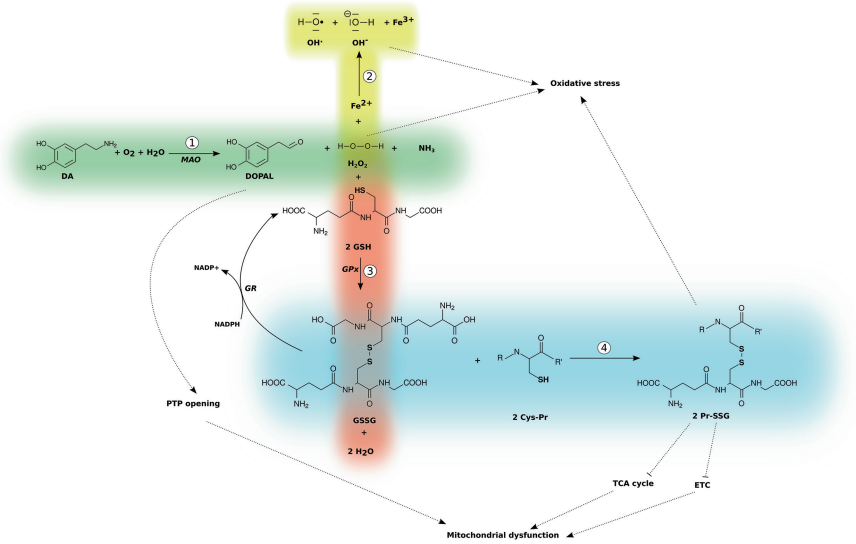


Fig. 2.4 Degradation of dopamine via MAO and induced toxicity. (*1*) The monoamine oxidase (MAO) catalyzes the oxidation of DA to DOPAL and produces H_2O_2 as by-product. High concentrations of DOPAL induce PTP opening and lead to mitochondrial dysfunction. (*2*) H_2O_2 can react with Fe^{2+} via the Fenton reaction and lead to the production of hydroxide ion and hydroxyl radicals which in turn increase oxidative stress levels within the cell. (*3*) H_2O_2 can be detoxified via the glutathione system. 2GSH will react with H_2O_2 to produce $2H_2O$ and GSSG via the glutathione peroxidase (GPx). GSSG is recycled into GSH by the action of GSH reductase (GR) using NADPH as a cofactor. (*4*) GSSG can react with free cysteinyl residues of proteins to form disulfide bonds. If this reaction occurs in the catalytic site of an enzyme, it can induce its inactivation. Proteins sensitive to this reaction include enzymes involved in the tricarboxylic acid (TCA) cycle or the electron transport chain (ETC), leading to the inactivation of these two pathways and ultimately to mitochondrial dysfunction. R and R′ represent the peptidic chain of the protein

Although at this stage H_2O_2 has been detoxified, the oxidized glutathione (GSSG) can spontaneously react with the thiol group of cysteinyl residues of proteins to form disulfide bonds. If a cysteinyl residue is located in the catalytic site of an enzyme, disulfide bonds formation leads to its inactivation. Enzymes shown to be inactivated this way include succinate dehydrogenase, NADH dehydrogenase, ATPase, isocitrate dehydrogenase, pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase, and aconitase [45]. The inactivation of these enzymes induces an inhibition of the tricarboxylic acid (TCA) cycle and the mitochondrial electron transport chain. Sulfhydryl modifications have also been shown to induce PTP opening and regulation [52].

PD is also associated with a higher dopamine turnover due to the lower number of dopaminergic neurons [53]. This induces a higher activity of MAO and thus an increase in MAO-associated toxicity. The increased turnover also promotes an increase in the autoxidation of dopamine and its metabolites which is described in the following section.

2.3.2 Autoxidation-Linked ROS Production

High intracellular concentrations of dopamine can lead to the formation of intermediate quinone products [44] (Fig. 2.5). These quinones can be produced either enzymatically or by autoxidation. The enzymatic formation of superoxide radicals or hydrogen peroxide increases the rate of CA oxidation [54]. Enzymes involved in the process include prostaglandin H synthase, lipoxygenase, and xanthine oxidase [55]. CA autoxidation can also occur in the presence of reactive nitrogen species that are derived from nitric oxide (NO) [56]. NO is synthesized in the central nervous system by the neuronal nitric oxide synthase (nNOS) as a mediator of the response to excitatory amino acids [57].

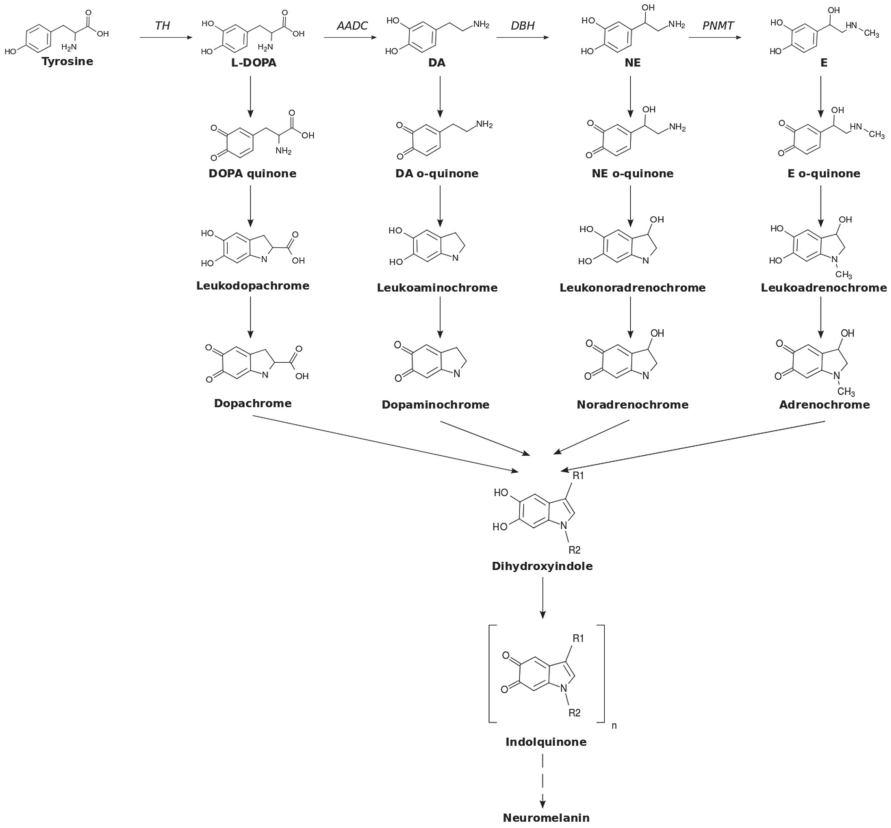


Fig. 2.5 Autoxidation of CAs. The synthesis of epinephrine from tyrosine occurs enzymatically as described in Fig. 2.1. Each of the metabolites of the CA synthesis pathway can auto-oxidize and form the respective quinones. Quinones then cyclize into leuko chrome intermediates, which further oxidize into chrome intermediates. The next step in the pathway is the formation of dihydroxyindole which oxidizes to form indolequinone which can polymerize to form neuromelanin. Depending on the precursor, R1 represents either H or OH and R2 represents H or CH_3

All products of the CA synthesis pathways are prone to oxidation, including epinephrine and norepinephrine. Products of dopamine oxidation include dopamine-*o*-quinone that cyclizes irreversibly to form leukoaminochrome and dopaminochrome. The oxidation pathways converge to dihydroxyindole and then to indole quinones that can polymerize to form neuromelanin [58].

Oxidation reactions producing CA quinones lead to the activation of proteases and lipases, irreversible inactivation of COMT, and an increase in cytosolic calcium concentration [56]. Quinones also impair mitochondrial function [55]. They are electron-deficient and react with nucleophiles such as cysteines, reduced glutathione (GSH), and cysteinyl residues of proteins to form 5-cysteinyl-dopamine [55].

The formation of quinone intermediates is reversible and can be prevented by antioxidants such as the GSH/GPx-system or simply cysteine due to its thiol group or by ascorbate [55]. However, once quinones have been formed, they can either be used as substrates by the NAD(P)H:quinone oxidoreductase (DT diaphorase) (two-electron reduction) or by the NADPH cytochrome P450 reductase (one-electron reduction) [54, 59] (Fig. 2.6). The action of the DT diaphorase leads to the production of leukochromes that are more redox stable and can subsequently be secreted [60]. This enzyme thus bypasses the semiquinone intermediate produced by the NADPH cytochrome P450 reductase. Semiquinone intermediates rapidly oxidize in the presence of oxygen to form back the quinone and superoxide anion radicals [59]. Other enzymes involved in quinone detoxification include sulfotransferases, COMT, or superoxide dismutase (SOD) [56]. Another important class of enzymes involved in quinone detoxification is metallothioneins. Their primary function is to maintain metal homeostasis by binding to heavy metals. As the name suggests, these proteins are containing a big amount of cysteinyl residues that can make up to 40 % of the total protein content [55].

Many enzymes contain cysteinyl residues playing a critical role in their function. The formation of 5-cysteinyl-dopamine has been shown to interfere with the activity of enzymes of the dopamine synthesis and transport pathways such as TH, dopamine transporter (DAT) [55], or dihydropteridine reductase (DHPR) [61]. These enzymes are crucial since TH is the rate-limiting step in dopamine synthesis and DAT regulates the duration and magnitude of dopamine signaling at the extracellular level and the dopamine concentration at the intracellular level [62]. DHPR is the enzyme responsible for BH_4 recycling, which is an important cofactor for TH, but also for phenylalanine hydroxylase (converting phenylalanine to tyrosine) as well as the tryptophan hydroxylase (first enzyme of the serotonin synthesis pathway) [52]. The inhibition of these enzymes under oxidative stress conditions contributes to cell protection by decreasing the intracellular amounts of dopamine and thus limiting its toxicity.

A protein that has been shown to be associated with PD is also affected: α-synuclein. This protein is initially produced in a soluble form. In order to form fibrils, it is aggregated to an intermediate state, the protofibrils. These protofibrils are toxic when not processed and accumulate to form Lewy bodies in PD patients. Although this protein does not contain cysteinyl residues, quinones are thought to affect its tyrosine and lysine residues. This formation of quinone–protein complexes

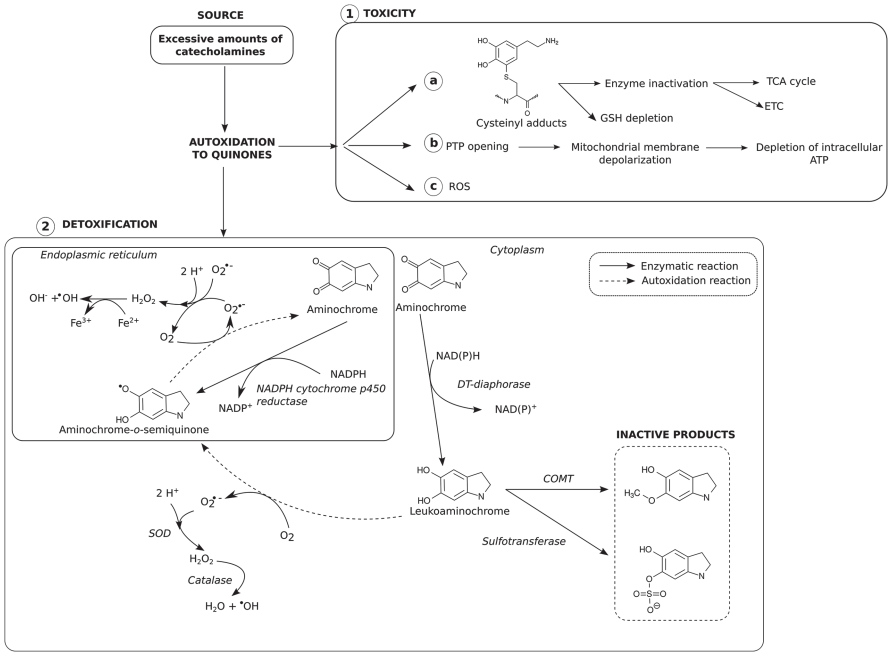


Fig. 2.6 Cytotoxicity and degradation of quinones. Excess of dopamine not transported into vesicles can auto-oxidize in the cytosol to form quinones (Fig. 2.5). (*1*) Toxicity. (*a*) Dopamine-*o*-quinone can react with cysteinyl residues of proteins. If these residues are located in the catalytic site of an enzyme, it leads to its inactivation. Affected enzymes include succinate dehydrogenase, NADH dehydrogenase, ATPase, isocitrate dehydrogenase, pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase, and aconitase. Dopamine-*o*-quinone can also react with the cysteinyl residue of GSH, which subsequently cannot be used as antioxidant anymore leading to GSH depletion. (*b*) Oxidation of quinones also induces the opening of the permeability transition pore (PTP) thus increasing the permeability of the inner mitochondrial membrane. This causes a proton leak across the membrane which leads to an uncoupling of ATP synthesis and ultimately to ATP depletion. (*c*) The autoxidation process consumes oxygen and produces superoxide radicals which contribute to the increase in intracellular reactive oxygen species (ROS). (*2*) Detoxification. Enzymes involved in the detoxification are the NADPH cytochrome p450 and the DT diaphorase. The former is located in the endoplasmic reticulum and uses NADPH to catalyze the one-electron reduction of aminochrome to aminochrome-*o*-semiquinone. The aminochrome-*o*-quinone can auto-oxidize back to aminochrome and generate superoxide radicals. Superoxide radicals and hydrogen peroxide induce an increase in the autoxidation rate. In the cytoplasm, the DT diaphorase uses the same substrate, but converts it to leukoaminochrome via a two-electron reduction reaction. This enzyme can use both NADH and NADPH. Leukoaminochrome can auto-oxidize to aminochrome-*o*-quinone, but in the cytosol this can be prevented by the superoxide dismutase (SOD) and catalase which remove superoxide radicals and hydrogen peroxide, thus decreasing the rate of autoxidation. Finally, catechol-*o*-methyltransferase and sulfotransferase can inactivate leukoaminochrome by covalent modification which can then be secreted

prevents the conversion of the protofibrils to fibrils, thus leading to an accumulation of the toxic protofibrils in the cytoplasm [55].

On the other hand, another protein associated with PD has a protective effect over quinone toxicity: Parkin is an E3 ubiquitin ligase. Its function is to recognize sub-

strates and promote their ubiquitination, thus targeting them for degradation by the ubiquitin–proteasome pathway [63]. Knockdown of the enzyme induced accumulation of dopaminochrome and apoptotic death in a neuronal cell model [55].

As discussed in the previous section, many enzymes of the TCA cycle and the mitochondrial electron transport chain are affected by modification of cysteinyl residues [45]. Furthermore, 7-(2-aminoethyl)-3,4-dihydro-5-hydroxy-2*H*-1,4-benzothiazine-3-carboxylic acid (DHBT-1), an oxidation product of 5-cysteinyl-dopamine, can also affect mitochondrial complex I [55].

Exposure to dopamine quinones has also been reported to cause a proton leak across the inner mitochondrial membrane, thus uncoupling ATP synthesis. This leads to respiration without ATP production and in turn depletion of intracellular ATP levels [52].

Oxidation products of dopamine do not only affect neurons but also activate microglia and induce expression of neurotoxic genes such as inflammation markers, cytokines, prostaglandins, and chemokines. On the other hand, quinones also induce a downregulation of the neuroprotective genes P2X and of the sestrin 1 gene which is responsible for balancing antioxidant levels, thus contributing to an increase in oxidative stress [64].

Several drugs have been identified to protect against quinone-mediated toxicity. One class includes DT diaphorase activators, such as 3-*tert*-butyl-4-hydroxyanisole (BHA), *tert*-butylhydroquinone, or dimethyl fumarate which also activates the GSH S-transferase and GSH reductase. Another class of compounds protecting against quinone-mediated toxicity is the nonsteroidal anti-inflammatory drugs (NSAIDs). Their main role is to protect against inflammation, but they also have been shown to inhibit the activity of prostaglandin H synthase, thus preventing quinone formation [55].

2.3.3 Permeability Transition Pores (PTPs)

One of the consequences of dopamine degradation, either via the activity of MAO or via autoxidation, is the induction of PTP opening. This is highly relevant since this opening can induce a loss of mitochondrial function and will thus be further discussed in this section.

PTPs are calcium-dependent protein channels that allow solutes smaller than 1500 kDa to cross the impermeable inner mitochondrial membrane. The perturbation of permeability induces the depolarization of the membrane potential, followed by the release of small solutes and finally proteins. The consequences are a swelling of the mitochondria and a loss of oxidative phosphorylation [52].

PTP opening is induced by oxidants and toxic quinones. In this case, the inner membrane permeability is increased, which leads to a proton leak across the membrane and thus, an uncoupling of ATP synthesis. This can be experimentally circumvented by the addition of cyclosporin A, which prevents PTP opening, highlighting the effect of quinones on PTPs [52].

Cysteinyl residues located in the active site of PTPs have also been implicated in their regulation, rendering these proteins sensitive to sulfhydryl modifications, such

as disulfide bond formation between quinones and cysteinyl residues of proteins [52]. Another regulator of PTP opening is the redox status of pyridine nucleotides. Oxidation of NADH and NADPH to NAD^+ and $NADP^+$ can induce pore opening. This shift can be achieved through the DT diaphorase enzyme, which detoxifies quinones via a two-electron reduction while oxidizing either NADH or NADPH [52].

Finally, it has been shown that PTP opening is also dependent on the activity of mitochondrial complex I [46]. If the activity of complex I is compromised as, for example, by the action of environmental toxins, PTPs will be more sensitive to DOPAL toxicity or the modification of cysteinyl residues.

2.3.4 L-DOPA Toxicity

L-DOPA is the direct precursor of dopamine. It was reported as such in 1938, although it had first been isolated in 1913 by Guggenheim who suggested that it was biologically inactive [65].

It was not before 1960 that dopamine deficiency was identified as the cause of the motor symptoms in PD and that subsequent intravenous injection of L-DOPA could transiently sooth the symptoms. The US Food and Drug Administration approved L-DOPA for PD treatment in 1970, and nowadays, it is still the most commonly used drug to cope with the symptoms. However, L-DOPA is not curing the disease, and 40–75 % of the patients under treatment will eventually redevelop motor symptoms within 4–6 years of L-DOPA therapy [65].

The efficacy of L-DOPA treatment versus direct dopamine administration is due to the fact that L-DOPA, in contrast to DA, can be transported across the blood–brain barrier (BBB) via the large neutral amino acid transport system. In order to increase the half-life of L-DOPA in the blood of the patients, it is commonly given in combination with AADC inhibitors such as carbidopa (which cannot cross the BBB), MAO inhibitors, or DA agonists [65].

The toxicity induced by L-DOPA treatment is similar to that induced by oxidation of DA: L-DOPA can also auto-oxidize and form reactive quinones that will contribute to an increase in oxidative stress [58]. Chronic L-DOPA therapy in rats reduces the activity of mitochondrial complex I. This is also the case when rats are treated with DA, but not with DOPAC or HVA, two products further down in CA metabolism [66].

Treatment with L-DOPA increases neuronal levels of DA but also of its downstream metabolites, including ROS formation. Since PD patients are treated with L-DOPA over long periods of time (years to decades), the permanent exposure might also affect other cell types in the body. Studies have shown that patients diagnosed with PD show a lower risk of developing most types of cancer [67]. However, an increase in cases of melanoma, a tumor of pigment-producing cells (melanocytes) in the skin, has been reported in patients with PD [68, 69]. One possible explanation for this correlation might be that melanocytes oxidize the administered L-DOPA and use it as a building block for eumelanin synthesis. The ROS produced

during these processes might over time lead to cancer development [70, 71]. There are indeed some studies which have indicated that the higher prevalence of melanoma in PD patients could be caused by long-term L-DOPA treatment [72, 73]. However, more recent cohort studies could not confirm this hypothesis [74, 75].

2.4 Astrocyte–Neuron Interactions

In the brain, dopaminergic neurons only account for 1–2 % of the total cell population [76]. While microglia are responsible for the immune surveillance in the brain, astrocytes are supporting other cell types by providing them with nutrients or protecting them against ROS-induced neurotoxicity [77]. Astrocytes and neurons interact in several ways (Fig. 2.7).

One of the examples of astrocyte–neuron cross talk is the astrocyte–neuron lactate shuttle hypothesis (ANLSH). This hypothesis states that during periods of high activity, such as hypoglycemia or hypoxia [78], astrocytes use anaerobic glycolysis to produce energy in the form of ATP and export lactate. Neurons can take up extracellular lactate via the monocarboxylate transporters (MCT) and oxidize it to pyruvate to fuel the TCA cycle. This shuttle is mediated by the glutamate release of neurons [79]. Glutamate is then taken up by astrocytes and induces aerobic glycolysis. This glutamate is converted to glutamine by the glutamine synthetase, an ATP-dependent enzyme absent in neurons, and then exported back for further neuronal use [77].

Astrocytes can also protect neurons from oxidative stress via a mechanism linked to their gap junction network [80], in particular via maintenance of calcium homeostasis. They have the highest antioxidant levels in the brain and can provide precursors for the GSH system to neurons [77]. GSH is a tripeptide formed from glutamate, cysteine, and glycine. It is known that astrocytes contain more GSH than neurons both in vitro and in vivo [81]. It is also interesting to note that most of the GSH produced by astrocytes is released [81]. Astrocytes can use several substrates for GSH synthesis such as exogenous amino acids, sulfur-containing compounds, or peptides. However, GSH can neither cross the blood–brain barrier nor the membrane of neurons. This is circumvented by the extracellular astrocytic expression of γ-glutamyl transpeptidase (γ-GT) that converts GSH into cysteinylglycine (CysGly). CysGly can then be used as substrate by the neuronal ectopeptidase aminopeptidase N (ApN) which breaks it into cysteine and glycine that can be imported into the neurons for subsequent GSH resynthesis. The needed glutamate can then be provided by the astrocytes in the form of glutamine recycled from uptaken neuron-released glutamate [81].

A last interesting point in the neuron–astrocyte interaction in the context of dopaminergic neurons is the ability of astrocytes to degrade dopamine. Upon neuronal depolarization, astrocytes can take up dopamine via DAT and subsequently degrade it via MAO and COMT. Moreover, astrocytes express high levels of GPx allowing them to cope with the toxicity of intracellular dopamine metabolism [77].

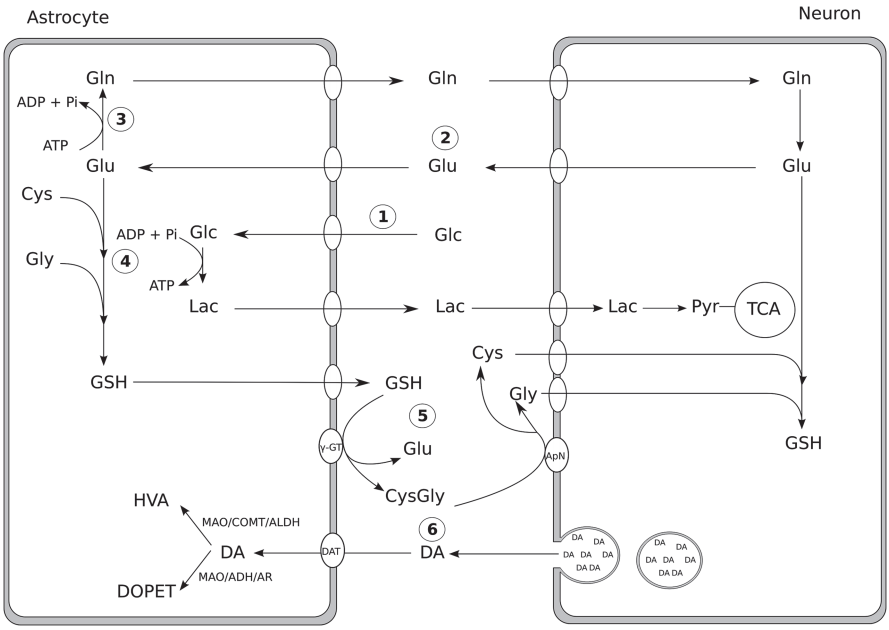


Fig. 2.7 Astrocyte neuron interactions. The metabolic interaction between neurons and astrocytes plays a pivotal role for neuronal survival. (*1*) The first interaction displayed is the astrocyte–neuron lactate shuttle hypothesis (ANLSH) which suggests that astrocytes take up glucose from the blood stream and use glycolysis to produce lactate and ATP. Lactate is then exported out of the cells where it is available for uptake by neurons. The neurons then take up lactate and oxidize it back to pyruvate which can enter the tricarboxylic acid (TCA) cycle to produce energy and activate the electron transport chain. (*2*) A second interaction between neurons and astrocytes is the glutamine–glutamate cycle. Neurons import glutamine and convert it to glutamate via glutaminase. Glutamate is an excitatory neurotransmitter or can be used as precursor for GSH synthesis. After release, glutamate is taken up by astrocytes, (*3*) converted back to glutamine via the glutamine synthase and exported for neuronal use or (*4*) used for GSH synthesis. In astrocytes, most of the GSH produced is exported for neuronal use. Neurons cannot import GSH as such, thus the gamma-glutamyl transpeptidase (γ-GT) cleaves it into glutamate and cysteinylglycine (CysGly) which can be further cleaved into cysteine and glycine via the neuronal aminopeptidase N (ApN) and finally imported into the neuron. (*6*) Another interaction between neurons and astrocytes is the recycling of dopamine (DA) after its release to the synaptic cleft. Astrocytes express COMT and MAO giving them the ability to degrade DA

2.5 Genetic and Environmental Factors Affecting DA Metabolism

This section highlights some of the genetic variation and environmental factors that affect specifically dopaminergic neurons. They can either cause the death of those neurons or be closely linked to the development of PD.

2.5.1 Genetic Factors

2.5.1.1 TH Deficiency

TH is the rate-limiting step in DA synthesis. TH knockout mice are not viable highlighting the importance of TH in prenatal development and postnatal survival [82].

TH impairment in vivo can be either due to a defect in the synthesis of its cofactor BH_4 or to a mutation in the TH gene itself. TH deficiency due to a mutation causes a neurometabolic disorder in which extracerebral production of CAs is not impaired. The symptoms can be improved by L-DOPA therapy, but the patients never reach adulthood [82]. A defect in BH_4 synthesis can arise from a deficiency in any of the enzymes involved in its synthesis pathway. BH_4 is a cofactor for TH, and thus its absence will impair CA production [83] and induce a developmental delay, hypokinesia, and progressive neurological deterioration [84].

2.5.1.2 DAT Genetic Variants

DAT is heavily involved in the duration and magnitude of extracellular DA signaling as well as for the maintenance of intracellular DA levels. Although it does not seem that genetic variations affect DAT expression, epidemiological studies have shown that a combination of certain variants with exposure to exogenous compounds such as fertilizers can increase the risk of developing PD three- to fourfold [85].

2.5.2 Environmental Factors

There are multiple chemicals that can target dopaminergic neurons and cause their degeneration. Here, we will discuss two compounds well known to induce PD in vivo: MPP^+ and rotenone.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a by-product of the chemical synthesis of the opioid analgesic 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP). When ingested, it causes irreversible damage to dopaminergic neurons of the SN and to a lesser extent to other catecholaminergic neurons [86], leading to a parkinsonism syndrome which includes the motor symptoms of PD. MPTP, however, is not the active form of the toxin: when it reaches the brain, it is taken up by astrocytes and metabolized via MAO B to 1-methyl-4-phenylpyridinium (MPP^+) [87]. MPP^+ can then enter dopaminergic neurons via DAT where it leads to cell death, most probably by complex I inhibition. A similar mode of action is accounted to the widely used pesticide rotenone. Although it is highly hydrophobic and thus able to cross the cell membrane of almost any cell, it seems to mainly affect dopaminergic neurons [88].

MPP^+ and rotenone are selective and potent inhibitors of mitochondrial complex I, the NADH dehydrogenase. Their toxicity leads to the expression and aggregation of

α-synuclein to Lewy bodies, a hallmark of PD. Both compounds also induce PTP opening and the consequent loss of membrane potential followed by impaired oxidative phosphorylation in combination with increased ROS production [89]. However, the production of ROS following complex I inhibition does not seem to be sufficient to cause the selective death of dopaminergic neurons [90]. Rotenone and MPP^+ also induce microtubule depolymerization [91]. The depolymerization of the microtubules leads to accumulation of vesicles in the soma that cannot be transported through the axon to the synapse. This does not seem to be affecting GABAergic or glutamatergic neurons, but it promotes selective degeneration of dopaminergic neurons [92]. Although all cell types enclose their neurotransmitters into vesicles which are transported across the cell via the microtubule network [92], GABA and glutamate are not readily converted into toxic intermediates. Moreover, it was shown that rotenone can induce a redistribution of DA from vesicles to the cytosol, thus increasing the concentrations of cytosolic DA as well as its autoxidation and MAO-induced degradation [93].

The fungicide benomyl has been associated with risks of developing PD and, like rotenone or MPP^+, can also induce microtubule disassembly. A more important effect in the scope of dopamine metabolism is its capacity to inhibit ALDH, an enzyme important in oxidizing toxic aldehydes including DOPAL. It has been shown that DOPAL is 400-fold more toxic than DA or DOPAC, due to its high potential to form quinones. In postmortem brains of PD patients, the concentration of DOPAL measured was four times higher than the concentration of DA [94].

2.6 Summary

Due to their chemical nature, dopamine and its metabolites are easily oxidized—a process often accompanied by the production of reactive oxygen species. While the MAO-mediated degradation of dopamine leads to the formation of hydrogen peroxide, the autoxidation of many intermediates of dopamine metabolism produces highly reactive quinones. These quinones can bind to cysteinyl residues of reduced GSH or proteins, leading to their inactivation if this residue is located in the active site of a protein. One way to overcome this problem is to increase production or uptake of antioxidants such as GSH or ascorbate. Interaction with astrocytes is an important fact for dopaminergic neuron survival: astrocytes provide the neurons with the GSH-precursor glutamine and are able to degrade excessive dopamine released by neurons. In dopaminergic neurons, excessive amounts of catecholamines can also be inactivated by their polymerization to neuromelanin. This polymer pigment itself can, however, have both a protective or deleterious effect, depending on the cellular context. It should be noted that although L-DOPA still represents the state-of-the-art treatment for Parkinson's disease, it also represents a catecholamine that can contribute to oxidative stress in already damaged dopaminergic neurons. Oxidative damage outside the brain induced by longtime L-DOPA treatment (e.g., in melanocytes) has often been discussed; however, there is little clinical evidence for that theory.

Finally, dopamine metabolism can be altered by genetic factors such as tyrosine hydroxylase deficiency or genetic variants of the dopamine transporter, as well as environmental factors such as pesticides or drugs.

Funding This project was supported by the Fonds National de la Recherche (FNR) Luxembourg (ATTRACT A10/03, THActivity CORE and AFR 5782260).

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Mitochondrial Mechanisms of Degeneration and Repair in Parkinson's Disease

Buhlman, L.M. (Ed.)

2016, XII, 275 p. 28 illus., 23 illus. in color., Hardcover
ISBN: 978-3-319-42137-7