HHS Public Access

Author manuscript

J Neural Transm (Vienna). Author manuscript; available in PMC 2023 November 27.

Published in final edited form as:

J Neural Transm (Vienna). 2020 February ; 127(2): 169–177. doi:10.1007/s00702-019-02106-9.

The catecholaldehyde hypothesis: where MAO fits in

David S. Goldstein[1]

[1]Autonomic Medicine Section, Clinical Neurosciences Program, Division of Intramural Research, National Institute of Neurological, Disorders and Stroke, National Institutes of Health, 9000 Rockville Pike MSC-1620, Building 10, Room 8N260, Bethesda, MD 20892-1620, USA

Abstract

Monoamine oxidase (MAO) plays a central role in the metabolism of the neurotransmitters dopamine, norepinephrine, and serotonin. This brief review focuses on 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is the immediate product of MAO acting on cytoplasmic dopamine. DOPAL is toxic; however, normally DOPAL is converted via aldehyde dehydrogenase (ALDH) to 3,4-dihydroxyphenylacetic acid (DOPAC), which rapidly exits the neurons. In addition to vesicular uptake of dopamine via the vesicular monoamine transporter (VMAT), the two-enzyme sequence of MAO and ALDH keeps cytoplasmic dopamine levels low. Dopamine oxidizes readily to form toxic products that could threaten neuronal homeostasis. The catecholaldehyde hypothesis posits that diseases featuring catecholaminergic neurodegeneration result from harmful interactions between DOPAL and the protein alpha-synuclein, a major component of Lewy bodies in diseases such as Parkinson disease, dementia with Lewy bodies, and pure autonomic failure. DOPAL potently oligomerizes alpha-synuclein, and alpha-synuclein oligomers impede vesicular functions, shifting the fate of cytoplasmic dopamine toward MAO-catalyzed formation of DOPAL—a vicious cycle. When MAO deaminates dopamine to form DOPAL, hydrogen peroxide is generated; and DOPAL, hydrogen peroxide, and divalent metal cations react to form hydroxyl radicals, which peroxidate lipid membranes. Lipid peroxidation products in turn inhibit ALDH, causing DOPAL to accumulate—another vicious cycle. MAO inhibition decreases DOPAL formation but concurrently increases the spontaneous oxidation of dopamine, potentially trading off one form of toxicity for another. These considerations rationalize a neuroprotection strategy based on concurrent treatment with an MAO inhibitor and an anti-oxidant.

Keywords

Monoamine oxidase; Dopamine; DOPAL; Alpha-synuclein

Introduction

Monoamine oxidases (EC 1.4.3.4) are flavin-containing enzymes that use oxygen to remove amine groups from monoamines such as serotonin and the catecholamines

✉ David S. Goldstein, goldsteind@ninds.nih.gov.

dopamine, norepinephrine, and adrenaline. In the process hydrogen peroxide, ammonia, and monoamine aldehydes are generated. The reaction of MAO with cytoplasmic dopamine results in the formation of the catecholaldehyde 3,4-dihydroxyphenylacetaldehyde (DOPAL).

In monoaminergic neurons MAO is present in the outer mitochondrial membrane. The enzyme occurs in two isoforms, MAO-A and MAO-B (Youdim and Riederer 2004). The genes encoding these isoforms are located next to each other on the X-chromosome. Although most of MAO activity in the brain is of the B type, MAO-A figures prominently in the oxidative deamination of striatal dopamine (Demarest and Moore 1981; Wachtel and Abercrombie 1994; Dyck et al. 1993; Kumagae et al. 1991; Colzi et al. 1990); however, administration of drugs that are selective MAO-B inhibitors in vitro can inhibit MAO-A in vivo (Eisenhofer et al. 1986; Fowler et al. 2015).

MAO plays key roles in the metabolism of endogenous monoamines. This review focuses on DOPAL, the immediate product of MAO acting on cytoplasmic dopamine. Although essentially all of the metabolism of neuronal dopamine passes through DOPAL, the literature on DOPAL is scanty, with only a bit over 100 articles culled from PubMed, in contrast with more than 150,000 articles on dopamine and more than 20,000 on MAO.

DOPAL toxicity

As for all endogenously produced aldehydes, DOPAL is toxic. Probably the first report describing DOPAL toxicity was that by Mattammal et al. (1995). Incubation of rat pheochromocytoma PC12 cells with 6.5 μM DOPAL for 24 h resulted in withdrawal of neurites and cell death; and exposure of mesencephalic cultures to 33 μM DOPAL evoked loss of tyrosine hydroxylase (TH)-positive neurons and a reduced fiber network. Subsequent reports by Burke et al. (Kristal et al. 2001; Li et al. 2001; Burke et al. 2003, 2004; Panneton et al. 2010) noted substantial cytotoxicity and neurotoxicity. In energetically compromised mitochondria from PC12 cells, DOPAL was more than 1000 times as potent as dopamine in inducing the mitochondrial permeability transition pore protein, a harbinger of cell death (Kristal et al. 2001). DOPAL reacts with hydrogen peroxide (produced concurrently with DOPAL when MAO metabolizes cytoplasmic dopamine) to form hydroxyl radicals (Li et al. 2001). Hydroxyl radicals peroxidate lipid membranes, and the lipid peroxidation product 4-hydroxynonenal inhibits aldehyde dehydrogenase (ALDH), promoting DOPAL accumulation (Florang et al. 2007)—one of several potential vicious cycles that could threaten homeostasis in dopaminergic neurons. In rats, DOPAL microinjection into the substantia nigra reduces counts of TH-positive neurons and evokes rotational behavior indicating nigrostriatal dopamine deficiency (Panneton et al. 2010).

MAO and ALDH in series help keep cytoplasmic dopamine levels low

In rat striatum, endogenous DOPAL is formed from the action of MAO-A on cytoplasmic dopamine (Fornai et al. 2000). Normally DOPAL is converted via aldehyde dehydrogenase (ALDH) to the acid 3,4-dihydroxyphenylacetic acid (DOPAC), which rapidly exits the

cells. In PC12 cells DOPAC is actively extruded via a sulfonylurea-sensitive transporter (Lamensdorf et al. 2000c).

Active uptake of cytoplasmic dopamine into vesicles via the vesicular monoamine transporter (VMAT) is not only required for dopaminergic neurotransmission but also serves as a detoxification mechanism (Gainetdinov et al. 1998; Fumagalli et al. 1999; Staal and Sonsalla 2000; Guillot and Miller 2009). This includes autotoxicity exerted by dopamine itself (Weingarten and Zhou 2001). Dopamine is well known to be prone to spontaneous oxidation to form a variety of oxidation products that are potentially toxic, including aminochrome (Munoz et al. 2012; Segura-Aguilar 2017) and 5-S-cysteinyldopamine (Cys-DA) (Badillo-Ramirez et al. 2019; Vauzour et al. 2010). As one would predict, animals with reduced vesicular uptake of dopamine have evidence of progressive nigrostriatal neurodegeneration (Caudle et al. 2007), while increased VMAT activity is neuroprotective (Lohr et al. 2014; Munoz et al. 2012).

One may conceptualize that MAO and ALDH act in series to keep cytoplasmic dopamine levels low (Fig. 1). MAO inhibition increases endogenous Cys-DA levels in guinea pig striatum (Fornstedt and Carlsson 1989) and in PC12 cells (Goldstein et al. 2016), consistent with a buildup of cytoplasmic dopamine.

The catecholaldehyde hypothesis

Given the toxicity exerted by exogenously administered DOPAL and the fact that DOPAL is produced continuously in catecholaminergic neurons, one may reasonably hypothesize that endogenous DOPAL acts as an autotoxin that contributes to catecholaminergic neurodegeneration. This is the essence of the “catecholaldehyde hypothesis” (Panneton et al. 2010).

A variety of animal studies have found that genetic abnormalities or environmental exposures that increase endogenous DOPAL levels result in catecholaminergic neurodegeneration. Pharmacologic inhibition of vesicular uptake increases endogenous DOPAL levels in PC12 cells (Goldstein et al. 2012), and mice with genetically determined low VMAT activity have aging-related loss of both nigral dopaminergic and locus ceruleus noradrenergic neurons (Caudle et al. 2007; Taylor et al. 2014); and mice with knockouts of cytosolic and mitochondrial ALDH have DOPAL buildup and nigrostriatal dopaminergic neurodegeneration (Wey et al. 2012).

In humans it has been reported that decreased ALDHA1A gene expression in blood is part of a “molecular signature” that can identify early PD (Molochnikov et al. 2012). ALDH1A1 gene expression and protein are decreased in substantia nigra specimens in patients with PD (Grunblatt et al. 2018; Mandel et al. 2005).

The complex I inhibitor rotenone decreases production of NAD^+, a required co-factor for ALDH. In PC12 cells rotenone increases endogenous DOPAL production (Lamensdorf et al. 2000a; Goldstein et al. 2015a), and DOPAL potentiates acute rotenone-induced cytotoxicity (Lamensdorf et al. 2000b). In the rats subacute administration of rotenone increases brain DOPAL levels and produces locomotor abnormalities resembling those in

Parkinson disease (unpublished observations). The fungicide benomyl also inhibits ALDH and builds up endogenous DOPAL (Casida et al. 2014), and farm chemicals inhibiting ALDH may contribute to the incidence of PD (Fitzmaurice et al. 2013, 2014; Ritz et al. 2016).

Clinical post-mortem studies have noted DOPAL buildup in the putamen in PD (Goldstein et al. 2011, 2013) and multiple system atrophy (Goldstein et al. 2015b, 2017b), both of which feature severe putamen dopamine deficiency (Kish et al. 1988; Goldstein et al. 2017b).

An almost completely independent line of research has implicated dopamine itself as an autotoxin, based on oxidation of dopamine to dopamine-quinone and then a variety of distal oxidation products (Fig. 2) (Carlsson and Fornstedt 1991; Weingarten and Zhou 2001; Dukes et al. 2005; Khan et al. 2005; Hasegawa et al. 2006; Bisaglia et al. 2007; Chen et al. 2008; Paris et al. 2009; Leong et al. 2009; Mosharov et al. 2009; Hastings 2009; Bisaglia et al. 2010; Surmeier et al. 2011; Wu and Johnson 2011; Jana et al. 2011a; Surh and Kim 2010; Lee et al. 2011; Gautam and Zeevalk 2011; Munoz et al. 2012; Bisaglia et al. 2013; Su et al. 2013; Banerjee et al. 2014; Cai et al. 2014; Herrera et al. 2017; Burbulla et al. 2017; Mor et al. 2017; Badillo-Ramirez et al. 2019). Some of these are known to be neurotoxic, such as aminochrome (Linsenbardt et al. 2009; Paris et al. 2009; Segura-Aguilar 2019), 5-S-cysteinyldopamine (Montine et al. 1997; Badillo-Ramirez et al. 2019), and isoquinolines (Storch et al. 2002; Nagatsu 1997). These compounds have in common that they evoke mitochondrial dysfunction (Jana et al. 2011b).

DOPAL–synuclein interactions

In 1997 three reports fundamentally changed concepts about mechanisms of catecholaminergic neurodegeneration. First, in a rare Greek-Italian-American kindred in which PD was transmitted as an autosomal dominant trait, the causal genotypic abnormality was identified—A53T mutation of the gene encoding the protein alpha-synuclein (AS) (Polymeropoulos et al. 1997). Second, Lewy bodies, a histopathologic hallmark of idiopathic PD, were found to contain abundant precipitated AS (Spillantini et al. 1997). Since then the view has evolved that PD as normally encountered clinically is a form of synucleinopathy. Other synucleinopathies include multiple system atrophy (MSA), in which AS is deposited in glial cytoplasmic inclusions in the brain (Wakabayashi et al. 1998); dementia with Lewy bodies (Baba et al. 1998); and pure autonomic failure (PAF) (Arai et al. 2000; Kaufmann et al. 2001).

All these forms of synucleinopathy entail chronic autonomic failure (Appenzeller and Goss 1971; Aminoff and Wilcox 1971; Rajput and Rozdilsky 1976), manifested in particular by neurogenic orthostatic hypotension (nOH) (Micieli et al. 1987; Benarroch 2003; Bonuccelli et al. 2003; Thaisetthawatkul et al. 2004; Jain and Goldstein 2012; Velseboer et al. 2011). In 1997 we reported the first evidence that Lewy body forms of nOH involve neuroimaging evidence of cardiac noradrenergic deficiency (Goldstein et al. 1997). The deficiency involves a combination of loss of myocardial sympathetic nerves (Amino et al. 2005; Orimo et al. 2006) and functional abnormalities in residual nerves—the “sick-but-not-dead” phenomenon (Goldstein et al. 2014, 2019).

DOPAL may be a key link between synucleinopathy and catecholaminergic neurodegeneration. The catecholaldehyde potently oligomerizes AS (Burke et al. 2008), and synuclein oligomers are thought to be the toxic form of the protein (Winner et al. 2011). Importantly, DOPAL-induced synuclein oligomers impede vesicular functions (Plotegher et al. 2017), which could set the stage for another vicious cycle. Divalent metal cations—especially Cu(II)—augment DOPAL-induced oligomerization of AS (Jinsmaa et al. 2014), while anti-oxidation with reduced glutathione, ascorbic acid, or N-acetylcysteine (NAC) attenuates the oligomerization (Follmer et al. 2015; Jinsmaa et al. 2018; Anderson et al. 2016). DOPAL-induced oligomerization of AS has been proposed to reflect condensation of two DOPAL molecules in a dicatechol pyrrole lysine adduct, followed by formation of isoindole linkages (Werner-Allen et al. 2016, 2018). Superoxide radical drives this process (Werner-Allen et al. 2017). Since superoxide is also generated when DOPAL oxidizes, this is another potential vicious cycle. A recent report supported the catecholaldehyde hypothesis, in that Schiff base adducts between DOPAL and the amines rasagiline or aminoindan were found to inhibit DOPAL-induced AS aggregation and toxicity (Kumar et al. 2019).

DOPAL also evokes the formation of quinone adducts with many proteins ("quinonization") relevant to catecholaminergic functions, including TH, L-aromatic-amino-acid-decarboxylase (LAAAD), and the type 2 VMAT—as well as AS. DOPAL is far more potent than dopamine in oligomerizing and quinonizing AS (Burke et al. 2008; Jinsmaa et al. 2018).

Oxidized dopamine can interact with AS (Hasegawa et al. 2006), promoting AS oligomerization (Lee et al. 2011; Saha et al. 2018; Leong et al. 2009). Aminochrome and 5,6-dihydroxyindole, products of dopamine oxidation, can also oligomerize AS (Huenchuguala et al. 2019; Munoz et al. 2015; Pham et al. 2009). Most investigations on this topic have not considered the possibility that dopamine-dependent AS oligomerization actually depends on production of DOPAL from dopamine via MAO (Lee et al. 2011; Leong et al. 2009; Hasegawa et al. 2006).

Recently we conducted a comprehensive assessment of the relative potencies of DOPAL and dopamine in oligomerizing and quinonizing AS (Jinsmaa et al. 2019). In both regards DOPAL was far more potent than dopamine. Even in the setting of evoked dopamine oxidation by Cu(II) or tyrosinase, dopamine did not quinonize AS. In cultured human oligodendrocytes DOPAL resulted in the formation of numerous intra-cellular quinoproteins that were visualized for the first time by near infrared microscopy. Of the two routes by which oxidation of dopamine modifies AS and other proteins, that via DOPAL therefore seems more prominent. Moreover, it stands to reason that given the alternatives of spontaneous oxidation of cytoplasmic dopamine vs. enzymatic oxidation catalyzed by MAO, the latter route would be favored.

Braak's "gut first" concept states that "a putative environmental pathogen capable of passing the gastric epithelial lining might induce AS misfolding and aggregation in specific cell types of the submucosal plexus and reach the brain via a consecutive series of projection neurons" (Braak et al. 2006). Almost half of the synthesis and metabolism of dopamine in the body takes place in non-neuronal cells of the gut (Eisenhofer et al. 1997). One may

speculate that DOPAL produced locally from abundant non-neuronal dopamine might react with AS to induce a pathogenic cascade.

Treatment implications of the catecholaldehyde hypothesis

Since MAO inhibition decreases DOPAL formation, a seemingly straightforward test of the catecholaldehyde hypothesis would be to determine whether MAO inhibitors slow the symptomatic progression of PD. Results of two large multicenter trials of the MAO-B inhibitors deprenyl (selegiline) and rasagiline, however, failed to demonstrate efficacy in this regard (Group PS 1996; Ward 1994; Fabbrini et al. 2012; Olanow et al. 2009; de la Fuente-Fernandez et al. 2010).

One can conceive of two potential explanations for this failure. First, the subjects in these clinical trials already had symptomatic PD, and the neurodegenerative process may already be advanced by the time symptoms occur. Second, MAO inhibition increases the spontaneous oxidation of cytoplasmic dopamine, as indicated by increased levels of Cys-DA (Fornstedt and Carlsson 1991; Goldstein et al. 2016)—the “MAOI tradeoff.”

The catecholaldehyde hypothesis has not yet been put to a direct test in humans. NAC does not interfere with the ability of the MAO-B inhibitor selegiline to decrease endogenous DOPAL production, while it attenuates the increase in Cys-DA induced by selegiline (Goldstein et al. 2017a), a reasonable strategy would be to combine NAC with an MAO inhibitor. A recent trial of oral and intravenous NAC alone reported retardation in the progression of symptoms of PD and of the striatal dopaminergic lesion (Monti et al. 2016, 2019).

Ideally, such a trial would involve patients with early disease or even people at risk for PD who have biomarkers of catecholaminergic neurodegeneration but without motor signs. Cardiac sympathetic neuroimaging evidence of myocardial noradrenergic deficiency and low cerebrospinal fluid levels of DOPA and DOPAC predict PD in at-risk individuals (Goldstein et al. 2018a, b). In patients with PD, the severity of the cardiac noradrenergic lesion progresses over time (Lamotte et al. 2019), and PAF can evolve into PD, DLB, or both (Kaufmann et al. 2017). By combining biomarkers of catecholaminergic dysfunction in extant neurons—the sick-but-not-dead phenomenon—with biomarkers of deposition of AS in sympathetic noradrenergic nerves (Isonaka et al. 2019), an enriched enough population may be identified for efficient testing of the catecholaldehyde hypothesis.

Acknowledgements

Research reported in this review was supported (in part) by the Intramural Research Program of the NIH, NINDS.

Abbreviations

ALDH	Aldehyde dehydrogenase
AS	Alpha-synuclein
Cys-DA	5-S-Cysteinyldopamine

DLB	Dementia with Lewy bodies
DOPAC	3,4-Dihydroxyphenylacetic acid
DOPAL	3,4-Dihydroxyphenylacetaldehyde
DOPAL-Q	DOPAL-quinone
LAAAD	L-Aromatic-amino-acid decarboxylase
MSA	Multiple system atrophy
NE	Norepinephrine
NET	Cell membrane norepinephrine transporter
nOH	Neurogenic orthostatic hypotension
OH	Orthostatic hypotension
PAF	Pure autonomic failure
PD	Parkinson disease
TH	Tyrosine hydroxylase
VMAT	Vesicular monoamine transporter

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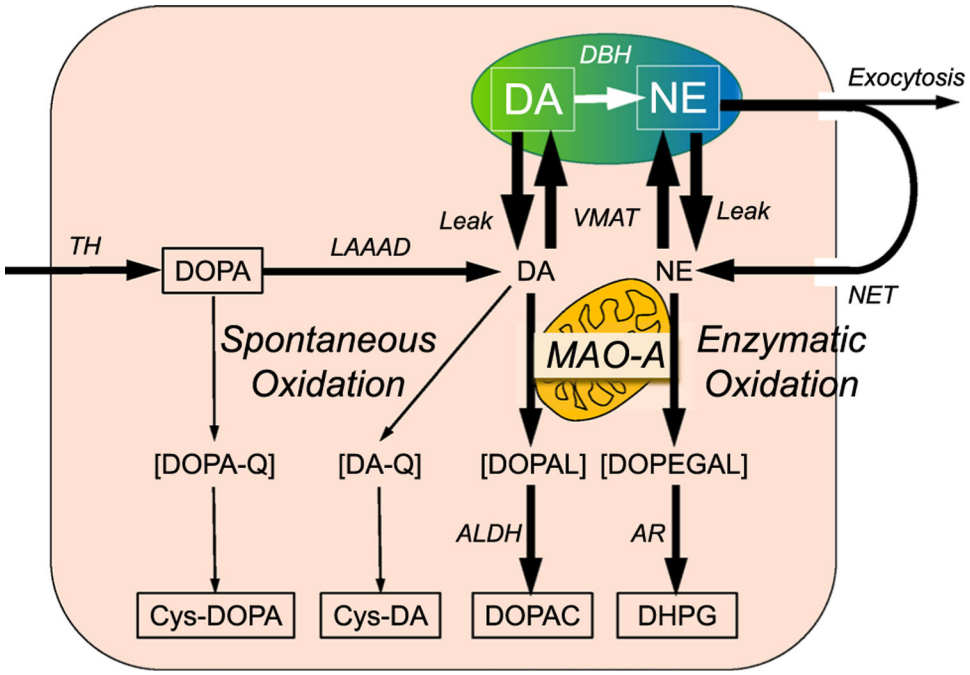

Fig. 1.

Overview of the sources and fate of intra-neuronal catecholamines, with emphasis on enzymatic oxidation catalyzed by MAO. Dopamine (DA) is produced in the cytoplasm via tyrosine hydroxylase (TH) acting on tyrosine to form 3,4-dihydroxyphenylalanine (DOPA) and then L-aromatic-amino-acid decarboxylase (LAAAD) acting on DOPA to form dopamine. Most of cytoplasmic DA is taken up into vesicles by way of the vesicular monoamine transporter (VMAT). Dopamine-beta-hydroxylase (DBH) in the vesicles catalyzes the production of norepinephrine (NE) from DA. Cytoplasmic DA is subject to oxidative deamination catalyzed by monoamine oxidase-A (MAO-A) in the outer mitochondrial membrane to form 3,4-dihydroxyphenylacetaldehyde (DOPAL), and NE is deaminated to form 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL). DOPAL is converted to 3,4-dihydroxyphenylacetic acid (DOPAC) via aldehyde dehydrogenase (ALDH), and DOPEGAL is converted to 3,4-dihydroxyphenylglycol (DHPG) via aldehyde/aldose reductase (AR). Most of vesicular DA and NE released by exocytosis is taken back up into the cytoplasm via cell membrane transporters—the NET for NE (although DA is a better substrate than NE for uptake via the NET). DOPA can undergo spontaneous oxidation to DOPA-quinone (DOPA-Q), resulting in formation of 5-S-cysteinylDOPA (Cys-DOPA), and DA can undergo spontaneous oxidation to DA-quinone (DA-Q), resulting in formation of 5-S-cysteinylDA (Cys-DA)

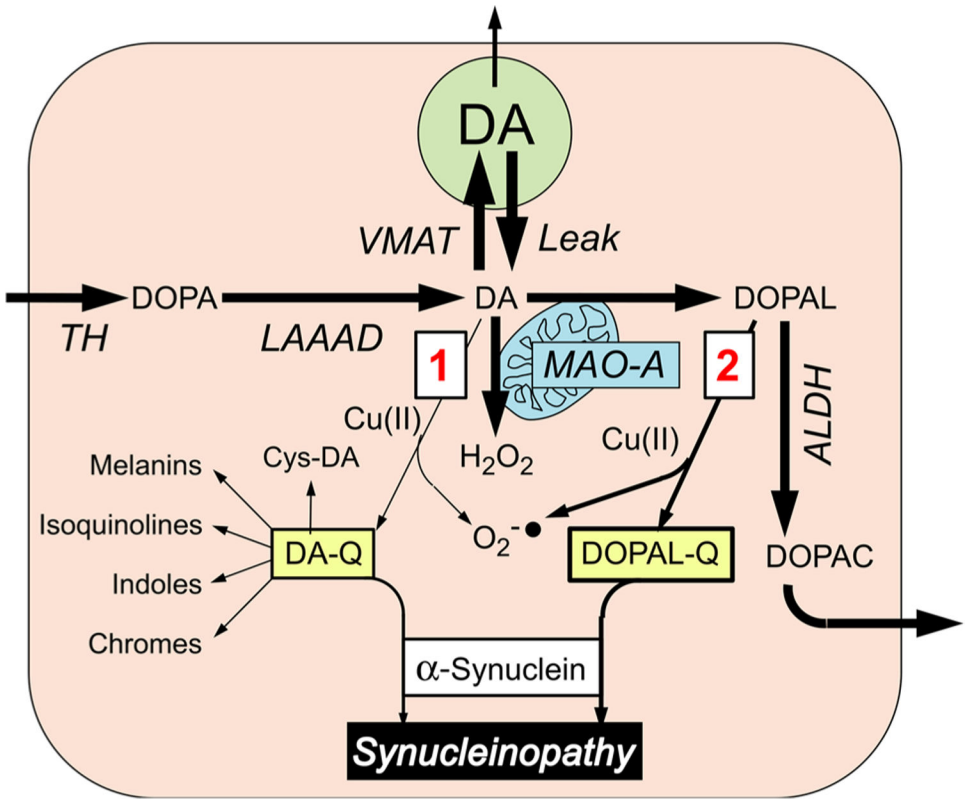

Fig. 2.

Alternative routes by which oxidation of cytoplasmic dopamine (DA) may modify alpha-synuclein. Most of cytoplasmic DA is taken up into vesicles via the vesicular monoamine transporter (VMAT); a minority undergoes oxidation, by two routes (red numbers in boxes). In route 1, DA is oxidized to form DA-quinone (DA-Q), with subsequent interactions with alpha-synuclein directly or via various further products of DA-Q, including 5-S-cysteinyldopamine (Cys-DA). In route 2, DA is oxidized enzymatically by monoamine oxidase-A (MAO-A) in the outer mitochondrial membrane to form 3,4-dihydroxyphenylacetaldehyde (DOPAL) and hydrogen peroxide (H_2O_2). Cu(II) promotes the oxidation of DA and DOPAL. Formation of DA-Q and DOPAL-Q is associated with generation of superoxide radicals ($O_2^{-\bullet}$). DOPAL is metabolized by aldehyde dehydrogenase (ALDH) to form 3,4-dihydroxyphenylacetic acid (DOPAC), which exits the cell