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Biogenic aldehyde-mediated mechanisms of toxicity in neurodegenerative disease

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Abstract

Oxidative decomposition of several biomolecules produces reactive aldehydes. Monoamine neurotransmitters are enzymatically converted to aldehydes via monoamine oxidase followed by further metabolism such as carbonyl oxidation/reduction. Elevated levels of aldehyde intermediates are implicated as factors in several pathological conditions, including Parkinson's disease. The biogenic aldehydes produced from dopamine, norepinephrine, and serotonin are known to be toxic, generate reactive oxygen species, and/or cause aggregation of proteins such as α-synuclein. Polyunsaturated lipids undergo oxidative decomposition to produce biogenic aldehydes, including 4-hydroxy-2-nonenal and malondialdehyde. These lipid aldehydes, some including an α,β-unsaturated carbonyl, target important proteins such as α-synuclein, proteasome degradation, and G-protein–coupled signaling. Overproduction of biogenic aldehydes is a hypothesized factor in neurodegeneration; preventing their formation or scavenging may provide means for neuroprotection.

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Keywords

DOPAL, Parkinson's disease, Aldehydes, ROS, Lipid peroxidation, DOPEGAL.

Abbreviations

4-HNE, 4-hydroxynonenal; 5-HIAL, 5-hydroxyindoleacetaldehyde; 5-HT, serotonin; ALDH, aldehyde dehydrogenase; AR, aldose reductase; aSyn, α-synuclein; CNS, central nervous system; DA, dopamine; DArgic, dopaminergic; DOPAL, 3,4-dihydroxyphenylacetaldehyde; DOPEGAL, 3,4-dihydroxyphenylglycoaldehyde; EPI, epinephrine; GPX, glutathione peroxidase; LC, locus coeruleus; MAO, monoamine oxidase; MDA, malondialdehyde; NE, norepinephrine; PD, Parkinson's disease; PT, permeability transition; ROS, reactive oxygen species; SN, substantia nigra.

Introduction

Spontaneous or enzymatic oxidation of various biomolecules produces aldehydes in the human body. Enzymatic oxidation of monoamine and indoleamine neurotransmitters yields reactive biogenic aldehydes. The oxidative decomposition of lipids (i.e., lipid peroxidation) likewise produces reactive biogenic aldehydes, some with α,β-unsaturated carbonyls. Cellular defenses of carbonyl metabolism include redundant enzymes, specifically, isoforms of aldehyde dehydrogenases, and compensatory systems, namely aldehyde reductases. Overwhelming or impairing aldehyde metabolism yields aberrant levels of such reactive species and is predicted to contribute to or exacerbate human disorders/degenerative conditions [1–4]. Given this, targeting the production or mitigating levels via scavengers of such biogenic aldehydes is predicted to be a therapeutic means to disease.

Oxidation of monoamine and indoleamine neurotransmitters

Monoamine oxidase metabolism can produce reactive aldehydes

Monoamine oxidase (MAO) metabolizes primary amines, such as the neurotransmitters norepinephrine (NE), epinephrine (EPI), serotonin (5-HT), and dopamine (DA), to produce a reactive biogenic aldehyde. MAO has two isoforms: MAO-A and MAO-B. Both isoforms can metabolize all four neurotransmitters and are located throughout the body, although MAO-A is present in the main production sites of NE, EPI, and DA: the locus coeruleus (LC), the rostral ventral lateral medulla, and substantia nigra (SN), respectively [5]. MAO-B is present mostly in glia and significantly contributes to monoamine metabolism of DA [6,7]. A 1952 review by Blaschko [8] proposed that the aldehydes produced from the metabolism of indoleamines and catecholamines by amine oxidases were toxic to the cells they were produced. This suggestion has evolved into the 'catecholaldehyde hypothesis' which proposes that the buildup of toxic aldehyde metabolites of neurotransmitters is a significant contributor to the pathogenesis of Parkinson's disease (PD) and potentially other neurodegenerative diseases that involve the loss of catecholamine neurons [9–12].

The aldehyde product of DA, 3,4-dihydroxyphenylacetaldehyde (DOPAL), is especially implicated in this toxicity. Other reactive aldehyde products include 3,4-dihydroxyphenylglycoaldehyde (DOPEGAL) from NE and EPI, and 5-hydroxyindoleacetaldehyde (5-HIAL) from 5-HT [5,13]. Alhough there is much less known about DOPEGAL and 5-HIAL than about DOPAL, it has been reported that both DOPEGAL and 5-HIAL are more reactive and toxic [5,14]. The loss of NE, EPI, 5-HT, and DA neurons have all been implicated in PD-related pathology [5]. Loss of DA neurons in the SN and NE neurons in the LC is linked to both motor and nonmotor symptoms in PD [5].

DOPEGAL, the aldehyde product of NE and EPI

NE is synthesized in the LC and is used as a neurotransmitter that promotes alertness in the central nervous system (CNS) [15]. In the sympathetic nervous system, it is used as a hormone in the blood stream [15]. EPI is formed in the rostral ventral lateral medulla and is used as a neurotransmitter in the CNS and as the primary hormone secreted by the adrenal medulla [5]. In the sympathetic nervous system, EPI is used as an excitatory modulator that increases blood flow, heart rate, and blood sugar.

The aldehyde product of both NE and EPI, DOPEGAL, is toxic to the cells it is produced in. Levels as low as 6 μM have been shown to kill PC-12 cells, and sympathetic ganglion cells undergo apoptosis when exposed to DOPEGAL [5,16]. It is possible that higher concentrations could induce necrosis [5,17]. A proposed mechanism of toxicity to explain the apoptosis observed after DOPEGAL exposure involves the permeability transition (PT) pore on the inner mitochondrial membrane. Induction of the PT pore causes the release of factors such as cytochrome *c*, which activates a downstream caspase cascade that triggers apoptosis [5,18–20]. When in the presence of Ca^{2+}, concentrations of DOPEGAL as low as 6 μM have been found to induce the PT pore [5,21]. The PT pore activation mechanism requires a reactive chemical species. When under oxidative stress, DOPEGAL produces a free radical, fulfilling this requirement [5,21]. DOPEGAL also induces cytosolic Ca^{2+}; apoptosis is associated with Ca^{2+} dysregulation [5,22].

5-HIAL, the aldehyde product of 5-HT

5-HT is synthesized in serotonergic terminals where it is used as a neurotransmitter in the CNS. 5-HT is implicated in many behaviors, such as feeding, affective disorders, sleep–wake cycles, motor system control, and reward [23]. 5-HT is enzymatically metabolized to the aldehyde 5-HIAL. A potential mechanism of toxicity of 5-HIAL is the oligomerization of α-synuclein (aSyn), and these oligomers are hypothesized to be involved in PD pathogenesis [13]. 5-HIAL generated *in situ* via 5-HT oligomerized aSyn *in vitro*, in PC12 cells, which could be blocked via addition of an MAO inhibitor [13].

DOPAL, the aldehyde product of DA

DOPAL is toxic to dopaminergic cells

DA is synthesized in the SN, ventral tegmental area, and hypothalamus. It is used as a neurotransmitter in the CNS [24]. Dopaminergic (DArgic) pathways include the nigrostriatal pathway, which is involved in motor control, and the mesolimbic pathway, which is involved in reinforcement and reward [24–26]. The aldehyde product of DA is DOPAL. DOPAL has been found to be toxic to DArgic cells at 7 μM, which is not far from *in vivo* concentrations of about 2 μM [27]. This could suggest that altering DOPAL metabolism even slightly can raise DOPAL to toxic levels [27].

DOPAL induces the PT pore in the presence of Ca^{2+}

DOPAL, similar to DOPEGAL, has been found to induce the mitochondrial PT pore in the presence of Ca^{2+} in concentrations as low as 125 nM [5,28]. The generation of a reactive chemical species is necessary for induction of the mitochondrial PT pore. It is claimed that DOPAL generates a hydroxyl radical when under conditions of oxidative stress; however, the generation of this free hydroxyl radical does not occur for DOPEGAL [5,29]. DOPAL and DOPEGAL could trigger induction independent of the free radicals produced, although the mechanistic target is not known. Whether the production of free radicals when under oxidative stress may exacerbate this issue or could be the primary cause of induction is not known.

DOPAL oligomerizes aSyn

DOPAL, similar to 5-HIAL, oligomerizes aSyn [13,30]. Werner-Allen et al. [31] demonstrated a unique chemical mechanism for this oligomerization via isoindole cross-linking *in vitro*. DOPAL binds covalently to the N-terminal lysine residues, potentially by a Schiff base and Michael addition adducts, which stabilizes the oligomer [32–35]. A large or small oligomer can form from this DOPAL interaction. The oxidation of DOPAL forms reactive oxygen species (ROS) which subsequently leads to the oxidation of the methionine residues on aSyn [32]. When all four possible methionine residues are oxidized, there is a reduction in the formation of large oligomers, which are more toxic than the small oligomers. This suggests that the methionine residues play a role in the neurotoxicity of DOPAL–aSyn interactions [32]. Furthermore, DOPAL has been shown to stimulate aSyn binding to tropomyosin receptor kinase B, leading to interference with neurotrophic activities, thereby increasing the susceptibility of neurons to degeneration [36].

DOPAL produces ROS and modifies proteins

The metabolism of DA by MAO generates DOPAL but also hydrogen peroxide, which can generate a toxic

hydroxyl radical via Fenton chemistry to damage proteins, DNA, and lipids [37]. In addition, DOPAL can auto-oxidize or be enzymatically oxidized to a reactive quinone, producing ROS such as superoxide anion [34,38,39]. It was proposed that DOPAL reacts with proteins through a Schiff base; however, recent evidence suggests a mechanism for protein modification involving Schiff base formation followed by oxidative rearrangement to an indole-type linkage [39–41]. Such a hypothesis may explain the following: (1) observed stability of the DOPAL adduct; (2) addition of sodium cyanoborohydride or antioxidants slows down or prevents protein modification by DOPAL; (3) reaction of DOPAL with proteins produces ROS [41].

Metabolism of biogenic aldehydes from monoamine and indoleamine neurotransmitters

Aldehydes are metabolized by aldehyde dehydrogenase

Typically, toxic aldehydes are metabolized by aldehyde dehydrogenase (ALDH). 5-HIAL is oxidized to 5-hydroxyindole acetic acid by ALDH [42]. DOPAL can undergo carbonyl oxidation to 3,4-dihydroxyphenylacetic acid by ALDH or reduction to the alcohol 3,4-dihydroxyphenylethanol by aldose reductase (AR) [43]. DOPEGAL is typically metabolized by AR to 3,4-dihydroxyphenylglycol and by ALDH to 3,4-dihydroxymandelic acid [43]. A decrease in ALDH activity is linked to PD-like pathology and behavior [44–46].

Aldehyde scavengers and DOPAL

Carnosine, a β-alanyl-histidine dipeptide, is found in the brain and myocardium in millimolar concentrations and may represent a novel scavenger of biogenic aldehydes such as DOPAL and DOPEGAL. Recently, carnosine was shown to block formation of catecholaldehyde protein adducts after NE exposure in isolated human cardiac mitochondria and, unlike GSH, form stable conjugates with DOPAL [47]. In addition, hydralazine has been proposed as a means to capture and detoxify biogenic aldehydes [41]. N-acetyl cysteine has also been shown to prevent oxidation of DA and to block DOPAL from reacting with proteins, perhaps via an antioxidant mechanism [12,39].

Oxidative decomposition of lipids

Lipid peroxidation produces lipid aldehydes

Another type of biogenic aldehydes implicated in disease are lipid aldehydes formed via lipid peroxidation. This process is generally initiated by free radicals [48,49]. These free radicals are increased in the presence of oxidative stress, which is thought to play a role in PD. Further mechanistic detail of lipid peroxidation and the formation of lipid aldehydes has been previously described [50,51]. The products of lipid peroxidation are lipid aldehydes, including 4-hydroxy-2-nonenal (4-HNE), malondialdehyde (MDA), and acrolein. Increases in lipid peroxidation products have been found in the brains of PD patients [52]. These lipid peroxidation products are often used as markers for oxidative stress; however, the precise mechanism in which lipid aldehydes contribute to the disease etiology of PD is not well understood [53]. Lipid aldehydes have been implicated in a variety of other diseases. This includes other neurodegenerative disorders—Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease—and neuropsychiatric disorders, cancer, diabetic complications, and liver disease [48,49,54].

The brain is susceptible to lipid peroxidation

Increases in lipid peroxidation products are seen in models of PD including exposure to rotenone, 6-hydroxydopamine, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [55–57]. This can be likened to the increase of lipid peroxidation seen in PD brains after death. The brain and especially DArgic neurons are more susceptible to lipid peroxidation, which is due in part to the brain's high energy demand, requiring a large amount of oxygen and mitochondria [58]. Oxygen in the brain can then aid in the autoxidation of catecholamines and catecholaldehydes leading to produce superoxide [38]. Furthermore, areas of the brain have increased levels of iron [59]. This iron can be used in the Fenton reaction to oxidize hydrogen peroxide to the hydroxyl radical and a hydroxyl anion. Both the hydroxyl radical and superoxide can lead to the initiation of lipid peroxidation. In healthy individuals, the brain maintains homeostasis through antioxidant enzymes which work to prevent damage by oxidative stress. Glutathione peroxidase (GPX) is one of these important detoxifying enzymes. Both GPX-1 and GPX-4 have been implicated in PD etiology. Whether this is due to a loss of enzyme activity or an upregulation of activity in response to oxidative stress is still unclear. GPX-4 expression has been found to be decreased in PD brains after death yet found to be increased when normalized to cell count [60]. More research is required, especially regarding GPX-4.

Lipid peroxidation is implicated in PD

Because most cases of PD are idiopathic, the exact cause for oxidative stress and increase in lipid peroxidation is not well understood. However, there has been progress in terms of how these lipid aldehydes contribute to the disease etiology of PD. 4-HNE has been shown to interact with aSyn and interfere with dopamine metabolism by inhibiting ALDH [40,61]. Furthermore, 4-HNE has been found to alter regulator of G-protein signaling 4 activity which is important for regulating G-protein–coupled receptors and is implicated as a potential therapeutic target for PD [62].

It has recently been found that 4-HNE not only reacts with aSyn but also leads to the release of pathogenic aSyn [63]. 4-HNE has been shown to interfere with

proteasome degradation and lysosomal function and is able to trigger extracellular vesicle release with intact protein [63,64]. Through treating primary neurons with 4-HNE and analyzing the extracellular vesicles secreted, an overall increase of aSyn and oligomeric aSyn in the 4-HNE−treated neurons was determined [63]. Although aSyn is most likely a protein important for mitochondrial function, its accumulation is a pathogenic hallmark of PD [61]. This process is one way in which lipid peroxidation products contribute to the disease etiology of PD. In addition, there may be an interplay or toxic synergy between the lipid peroxidation aldehydes and catecholaldehydes. Work in previous years found that both 4-HNE and MDA potently inhibit ALDH and/or AR metabolism of DOPAL, contributing to increases in the level of this biogenic catecholaldehyde, as discussed in the section Aldehydes are metabolized by aldehyde dehydrogenase [40,65−67]. As a result, neurotoxicity via lipid aldehydes such as 4-HNE and MDA may be augmented as the result of their ability to impede the carbonyl oxidation/reduction step for the metabolism of DA and other monoamines.

Comparison of biogenic aldehyde reactivity

The various biogenic aldehydes formed can vary in terms of origin (e.g., lipid) and tissue/cell type location as described previously but also demonstrate diversity of reactivity for rate and target nucleophile. The monoamine-derived aldehydes may primarily target amines, such as Lys or Arg, whereas the α,β-unsaturated aldehydes derived from lipids may primarily react with Cys/thiols. Although there may be several exceptions, under physiologic conditions, the reaction for monoamine-derived aldehydes such as DOPAL initially involve Schiff base chemistry followed by rearrangement or condensation while the α,β-unsaturated carbonyls (e.g., 4-HNE) modify Cys/thiols by Michael-type addition [31,33,41,68,69]. Reactivity rates may vary or be difficult to measure given the instability of the intermediate, such as observed for DOPEGAL which appears to degrade spontaneously and quickly [47]. A rate constant was measured for DOPAL modification of Lys/primary amine ($2\ M^{-1}\ min^{-1}$) and found to be 20- to 30-fold greater than that for the reaction of 4-HNE with Lys/primary amine [41,70]. However, 4-HNE and α,β-unsaturated carbonyls rapidly react with Cys/thiols ($>1\ M^{-1}\ s^{-1}$) while DOPAL does not [70].

Summary

The oxidative decomposition of biomolecules, such as neurotransmitters and lipids, produces a range of aldehyde-containing intermediates that vary in location (e.g., tissue/cell type, subcellular location) and reactivity. Normal, physiologic processes produce these species at levels controllable by carbonyl-metabolizing enzymes, and it is the aberrant and chronic overproduction of biogenic aldehydes that is hypothesized as an initiating factor for pathogenic events relevant to neurodegenerative disease. Mechanisms for cellular injury include formation of ROS, mitochondrial toxicity, modification of protein targets critical for survival of neurons, and aggregation/cross-linking of aSyn. Knowledge of such pathways for toxicity may yield biomarkers of early pathogenic events and therapeutic targets for neuroprotection.

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Conflict of interest

The authors declare no conflict of interest.

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