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REVIEW ARTICLE

Patients Stratification Strategies to Optimize the Effectiveness of Scavenging Biogenic Aldehydes: Towards a Neuroprotective Approach for Parkinson's Disease

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Abstract: Parkinson's disease (PD) is a clinically heterogeneous disorder with a multi-factorial pathology. Various molecular mechanisms are involved in the pathogenesis of PD, converging to oxidative stress and proteinopathy. The accumulation of reactive aldehydes (*i.e.*, the dopamine metabolite DOPAL, lipid-peroxidation products, and advanced glycation end-products) has been reported in PD patients' brains. Aldehydes easily react with primary amines such as lysine residues, which are involved in several regulatory processes in cells. Therefore, aldehyde adducts lead to severe consequences, including neuronal proteostasis, mitochondrial dysfunction, and cell death. In this review, we analyzed the scavenging role of amines toward toxic aldehydes in the brain. Interestingly, small molecules like metformin, rasagiline, hydralazine are already clinically available and used in the therapy for PD and other diseases. Hence, we propose to reevaluate this class of drugs as a disease-modifiers for PD, and we suggest that improved analysis of their pharmacology and bioavailability in the brain, together with a more precise patients stratification, should be considered before planning future clinical trials.

Keywords: Parkinson's disease, aldehyde, scavenger, neuroprotection, patients stratification, biomarkers.

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, and it currently affects about 1% of the population over 65 years old and more than 4-5% over 80 [1, 2]. According to the statistics provided by the Parkinson's Foundation, nearly 10 million people are currently suffering from PD (https://www.parkinson.org/Understanding-Parkinsons/Statistics), with a higher prevalence in Europe, North America, and South America [3].

The diagnosis of PD is currently based on the presence of typical motor manifestations (tremor at rest, rigidity, bradykinesia, and postural instability) and underlined by the progressive loss of the dopaminergic neurons of the nigrostriatal circuits in the midbrain [4, 5]. Additional non-motor features are also present, and some, like olfactory dysfunction, cognitive impairment, psychiatric symptoms, rapid-eye-movement sleep disorder, may precede the motor manifestations by many years [6]. Along with the disease progression, further complications arise, causing significant disability that can hardly be managed by the available therapeutic approaches.

The considerable heterogeneity among patients in the age of onset, symptoms, and progression reflects the multi-systemi and multi-factorial aspects of the pathogenesis of PD. There are diverse epidemiological variables like age, gender, and ethnicity, together with environmental as well as genetic variants, identified by genome-wide association studies (GWAS), which are considered risk factors [6, 7]. Most of the cases are classified as sporadic with an undefined etiology, but there are a fraction of monogenic forms (ranging from 5 to 10% among different world regions), with 19 disease-causing genes identified to date [8]. At the molecular level, in both genetic and idiopathic PD, several pathways are affected, that with few exceptions [9, 10] all converge to alpha-Synuclein (aSyn) aggregation and deposition in Lewy Bodies (LBs), lysosomal and mitochondrial dysfunction, oxidative stress, and neuroinflammation. According to the multiple-hit hypothesis for PD pathogenesis, many risk factors concomitantly affect neuronal homeostasis, where their synergistic action overcomes the homeostatic threshold and trigger the neurodegenerative process [11-13].

From a clinical perspective, such complexity in PD pathology still challenges the successful identification and development of disease-modifying interventions by specifically targeting the affected molecular pathways. The numerous currently available pharmacological and surgical interventions are mainly symptomatic and aim to replace the dopamine (DA) reservoir and action in the nigrostriatal pathway (DA precursor L-DOPA, DA agonists, inhibitors of DA catabolism).

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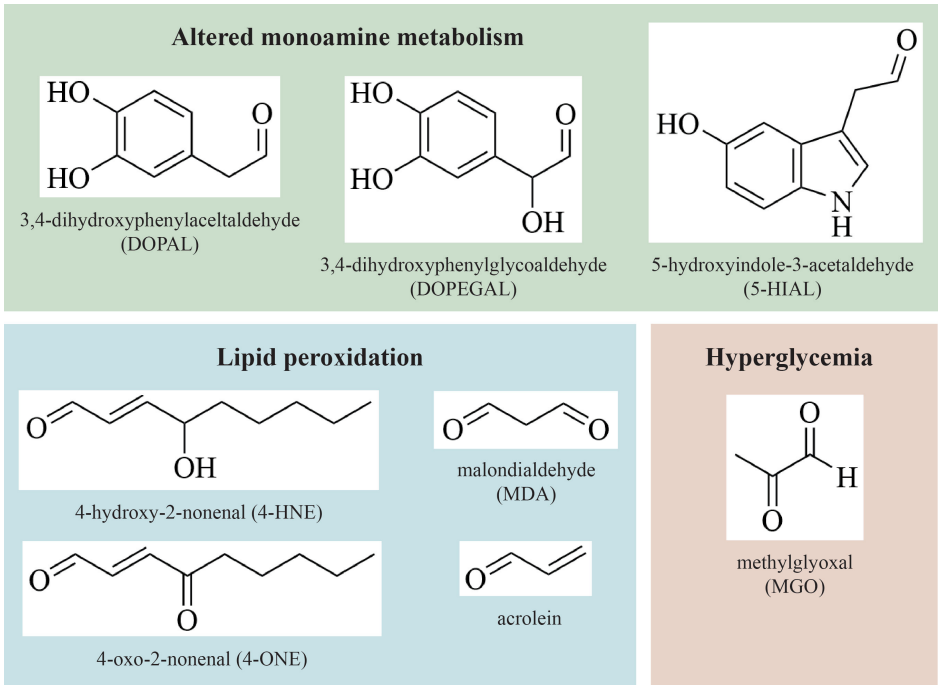


Fig. (1). Aldehydes of pathological relevance in Parkinson's disease. Among them, aldehydic intermediates derived from the catabolism of dopamine, norepinephrine, and serotonin (green); lipid peroxidation products (blue); glycating agent derived by glucose metabolism in diabetic condition (red). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In the present review, we discuss the potential benefits of the co-administration of antiparkinsonian agents with guanidine molecules to simultaneously target multiple processes. Small molecules like metformin, rasagiline, hydralazine, are already in clinical practice, and rasagiline has been extensively tested as a possible disease modifier in PD. Here, we point out their potential beneficial effect as scavengers of biogenic aldehydes whose aberrant accumulation and neurotoxicity have been described in PD [14-18]. Combined treatments with these drugs, together with an accurate evaluation of pharmacology and bioavailability in the brain and a precise patient stratification, might bring significant improvement in the definition of novel disease-modifying approaches for PD.

2. ALDEHYDES OF PATHOLOGICAL RELEVANCE IN PARKINSON'S DISEASE

Aldehydes are highly reactive molecules due to their electrophilic carbonyl groups. They undergo several reactions, such as nucleophilic additions that lead to the formation of alcohols, alkenes, diols, and cyanohydrins. Alternatively, the aldehyde moiety easily reacts with primary amines through a Schiff-base condensation producing imines. Hence, aldehydes have the intrinsic ability to irreversibly and covalently modify a variety of biomolecules in the cellular milieu, *i.e.*, proteins (typically on lysines, cysteines, histidines), nucleic acid, amino-phospholipids, and other small molecules. Unlike free radicals, aldehydes are relatively stable, and they can diffuse far from the site where they are first generated. Thus, under physiological conditions, the rapid conversion of the aldehyde to less reactive moieties is rapidly ensured by dedicated enzymes (aldehyde dehydrogenases, aldehyde reductases, alcohol reductases) before any toxic down-stream cascade could be triggered by the aldehyde addition to relevant targets.

Interestingly, several studies reported that the alteration of specific cellular pathways in PD and other co-existing pathological conditions leads to the accumulation of neurotoxic aldehydes in the brain. As listed in (Fig. **1**), alterations in the catabolic pathway of monoaminergic neurotransmitters (catecholamines and indoleamines) cause the accumulation of aldehydic intermediates as 3,4-dihydroxyphenylacetaldehyde (DOPAL) from DA, 3,4-dihydrophenylglycolaldehyde (DOPEGAL) from norepinephrine (NE), and epinephrine and 5-hydroxyondole-3-acetaldehyde (5-HIAL) from serotonin (5-HT). Also, as a consequence of the increased oxidative stress, lipid peroxidation generates sub-products like 4-hydroxy-2-nonenal (4-HNE), 4-oxo-2-nonenal (4-ONE), malondialdehyde (MDA), and acrolein. Moreover, the hyperglycaemia associated with PD patients with diabetic conditions causes increased glucose metabolism and consequently increased methylglyoxal (MGO) production.

2.1. Altered Monoamines Catabolic Pathway

Although the dopaminergic neurons of the *Substantia Nigra pars compacta* (SNpc) are among the most affected in PD, neurodegeneration progressively pervades other neighbouring regions, leading to extensive loss of norepinephriner-

gic neurons of the *locus coeruleus* (LC), the epinephrinergic neurons of the *rostral ventral lateral medulla* (RVLM) and the serotoninergic neurons of the *dorsal raphe nucleus* (DRN). The overall monoaminergic neuron loss correlates with the entire spectrum of PD symptoms, from motor dysfunction to sleep disorders, cognitive deficits, and altered emotional behaviours.

Of note, all these neuron subtypes share similar metabolic pathways of their monoaminergic neurotransmitters. However, several studies in PD patients' brains as well as PD experimental models pointed out an imbalance in monoamine homeostasis at multiple levels, identifying both genetic and environmental factors.

Under physiological conditions, DA and 5-HT are loaded in the synaptic vesicles as they are synthesized, whereas NE is produced in the lumen of the vesicles as the direct conversion of DA by the dopamine-β-hydroxylase enzyme. The small fraction of molecules that leaks from the vesicles rapidly undergoes catabolic conversion, starting with the oxidative deamination by monoamine oxidase (MAO) enzymes on the outer mitochondrial membrane to generate the aldehydic intermediates DOPAL, DOPEGAL, and 5-HIAL.

Conversely, post mortem studies on isolated synaptic vesicles from PD patients' brains revealed a decreased activity of about 90% of the vesicular monoamine transporter type 2 (VMAT2), which is responsible for vesicles loading with dopamine and serotonin [19, 20], thus resulting in increasing concentration of cytosolic monoamines. Coherently, *in vivo* mouse models with reduced expression and activity of VMAT2 by genetic knockdown or inhibition by the anti-hypertensive drug reserpine resemble many features of the pathophysiology of PD and the age-related degeneration of both SNpc and LC [21-24]. Interestingly, from the genetic point of view, some polymorphisms in the *Vmat2* gene have been associated with PD [25] and Infantile-Parkinsonism Dystonia 2, an infantile-onset movement disorder with severe parkinsonism, mood disturbance, and autonomic instability due to DA and 5-HT dyshomeostasis [26].

Once accumulated in the cytosol, DA and NE are oxidized by MAO-A (in the SNpc, LC, and RVLM neurons) [27], while 5-HT is reported to be metabolized by MAO-B in the DRN serotoninergic neurons [28]. Despite both MAO-A and MAO-B isoforms are expressed in SNpc dopaminergic neurons, MAO-B is abundantly expressed in striatal astrocytes [27, 29]. Once released in the synaptic cleft, a consistent fraction of DA is rapidly re-uptaken by the dopamine transporter DAT of astrocytes, where it is rapidly catabolized by MAO-B. Of note, an increased expression and activity of MAOs have been detected along with aging and neuroinflammation [30-33]. Also, a correlation between PD cases and some variants of the *Mao-B* gene, encoding for a hyperactive enzyme, has been described [34-36]. Hence, the upregulation of this first catabolic step results in sustained aldehydes production, together with the other by-product hydrogen peroxide, which likely exacerbates oxidative stress.

Increasing levels of DOPAL, 5-HIAL, and DOPEGAL have been found in PD patients' brains, where they were not promptly detoxified by the aldehyde dehydrogenases (ALDHs) into their less reactive carboxylic derivatives 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) and by the aldehyde reductases (ARs) into the ethanol form 3,4-dihydroxyphenylglycol (DOPEG) [14, 17, 37].

ALDH1A1 and ALDH2 are the most expressed enzymes responsible for dopamine catabolism in the dopaminergic neurons of SNpc. Of note, studies on post-mortem PD patients' SNpc revealed a significantly decreased expression and activity of ALDH1A1, assessing both at transcriptional and proteomic levels [38-41]. Consistently, the mouse model double knock-out for *Aldh1a1* and *Aldh2* shows an age-dependent loss of midbrain dopaminergic neurons, impaired motor performance, and increased striatal levels of DOPAL, 5-HIAL, and 4-HNE [42]. Although none of the *Aldh* genes have been reported in GWAS on PD [7], some variants and haplotypes have been associated with an increased risk to develop PD in Asian and American populations [43-46]. Additionally, ALDH2*2 mutant enzyme with no enzymatic activity, has been associated with cognitive impairments and sleep disturbances in PD patients [47, 48].

Environmental factors seem to play an important role in the accumulation of biogenic aldehydes. Many chemical compounds are known to be strong inhibitors of the ALDH enzymes [49]. Among them, drugs like the anti-alcohol abuse Disulfiram and Daidzin have shown to increased DOPAL and 5-HIAL concentration [18, 50, 51]. Importantly, heavy-dose consumption of Disulfiram by alcohol abusers has been associated with parkinsonism and enhanced toxicity in basal ganglia, thus corroborating the link among ALDH inhibition, degeneration of nigrostriatal axis, and PD [52]. Also, exposure to pesticides like Benomyl and Dieldrin (both irreversible inhibitors of ALDH2) are associated with an increased risk of developing PD in epidemiological studies [53, 54]. Finally, the ALDHs/ARs-mediated reactions rely on $NADP^+$/NADPH as a cofactor. Hence, any kind of insult that would affect the mitochondrial physiology (*i.e.*, complex I inhibition by rotenone exposure) and homeostatic level of the $NADP^+$/NADPH reservoir is likely to undermine the DOPAL, DOPEGAL, and 5-HT detoxification [55].

2.1.1. Dopal, Dopegal, and 5-HIAL Neurotoxicity

Physiological intermediates of catecholamines catabolism, DOPAL, and DOPEGAL have been described as an endogenous neurotoxin; this was first hypothesized by Blashko in 1952 and then further experimentally substantiated by Burke and others in the late 90s [14, 56]. DOPAL and DOPEGAL concentrations were estimated to be around 2-3μM in the SNpc and 1.4μM in the LC, respectively. However, concentrations higher than physiological (>6μM) have been described as a threshold to elicit cytotoxic effects in various cell lines [57].

The main DOPAL and DOPEGAL-associated toxicity described in both *in vitro* and *in vivo* models refer to mitochondrial dysfunction by triggering the mitochondrial perme-

ability transition pore [58], caspase, and apoptosis activation by calcium-mediated processes. Also, the ability to produce radical oxygen species (ROS) leading to oxidative stress and glutathione depletion has been described due to the tendency of the catechol group to self-oxidise to quinones. More recently, the ability of DOPAL to decrease cell viability, trigger apoptosis, and mitochondrial dysfunction has been assessed in an astrocytic cellular model [59].

A unique case is the synergy between the catechol and the aldehyde moieties of DOPAL, which is thought to enhance its reactivity towards proteins, targeting the thiol group of cysteines and the amino group of lysines [60-62]. Indeed, several studies highlight the ability of DOPAL to covalently modify a broad spectrum of targets triggering detrimental consequences for neuronal homeostases, such as enzyme inhibition (*i.e.*, tyrosine hydroxylase, TH) by modification of functional residues in the active site [63], protein cross-linking and aggregation [60, 64].

In this frame, the DOPAL-induced oligomerization of aSyn has been widely investigated, being aSyn aggregates majorly involved in PD pathogenesis. Indeed, the covalent modification of aSyn lysines (15 lysines out of 140 amino acids) by DOPAL triggers aSyn aggregation, leading to synapse dysfunction and neuronal vulnerability, as demonstrated in various *in vitro* and *in vivo* models [65-68]. Along the same line, DOPEGAL modification of Tau lysines was showed to trigger Tau aggregation in a cellular model and after injected in the LC of a mouse model [69]. Besides, both DOPAL and DOPEGAL had been demonstrated to activate the asparagine endopeptidase (AEP) in the SNpc and LC, respectively [69, 70]. AEP-mediated cleavage of aSyn at N103 and Tau at N368 triggered protein aggregation [69, 71], leading to aSyn and Tau pathology, progressive neurodegeneration, motor impairment, and cognitive dysfunction. Although DOPEGAL-induced Tau aggregation in the LC was primarily associated with Alzheimer's disease (AD), the alterations of the catecholamine metabolic pathway observed in PD might lead to similar DOPEGAL-dependent neurotoxicity in PD as well.

Finally, while 5-HIAL neurotoxicity was poorly investigated in PD models, the ability of 5-HIAL to covalently modify and trigger aSyn oligomerization was assessed [72].

2.2. Oxidative Stress and Lipid Peroxidation

Among the consequences of oxidative stress, the unregulated oxidation of polyunsaturated fatty acids (PUFAs) by free radicals represents a major issue in PD. The increasing levels of hydroxyl and superoxide radicals trigger the lipid peroxidation of PUFAs (*i.e.*, arachidonic and linoleic acid) with further production of several reactive intermediates like 4-HNE, 4-ONE, MDA, and acrolein [73]. Being PUFAs the major component of membranous structures in all cells, the toxic action of lipid peroxidation products may lack specificity for neurons that are more affected in PD. Moreover, neurons in the SNpc are known to be particularly susceptible to oxidative stress due to the considerable energy demand that challenges the mitochondrial integrity, the lower antioxidant defences, and the catechol tendency to autoxidation [74]. Hence, the generation of lipid peroxidation products and the associated neurotoxicity are expected to be exacerbated in catecholaminergic neurons in PD.

Indeed, several studies on post-mortem PD patients' brains pointed out the accumulation of 4-HNE-protein adducts in the nigrostriatal neurons and LBs [16, 75]. Similarly, rat models of PD injected with 6-OHDA displayed significantly increased MDA concentration and acrolein-bound proteins, specifically in the striatum [76, 77]. Also, the 4-HNE and MDA content in plasma and cerebrospinal fluid of PD patients was found to be significantly higher compared to healthy subjects, thus hinting at their quantification as potential biomarkers for PD [16, 78-80].

As for the monoamine-derived aldehydes, lipid peroxidation products are usually metabolized by ALDHs-mediated oxidation, reducted by ADHs, or conjugated with glutathione (GSH) [81]. However, in PD, ALDHs frequently display reduced expression and activity as described above, thus hindering the rapid 4-HNE and MDA detoxification. Coherently, a double knock-out mouse model lacking ALDH1A1 and glutathione peroxidase-1 (GPX1) displayed an age-related decrease in motor performance and accumulation of 4-HNE protein adducts [82]. Besides, concentrations of both 4-HNE and MDA up to 100μM were reported to strongly bind the catalytic site of ALDH1A1 and ALDH2 and to inhibit their activity both *in vitro* and in cellular models [64, 83, 84]. Hence, the aldehyde detoxification capacity of neurons is seriously compromised, leading to increasing levels of DOPAL and other biogenic aldehydes in a loop that exacerbates toxicity.

2.2.1. Neurotoxicity of Lipid Peroxidation Products

While the physiological concentration of lipid peroxidation products like 4-HNE varies between 0.1-3μM, it has been reported that under pathological conditions, it increases to 0.01-5mM [85]. As for other aldehydes, lipid peroxidation products have a very broad spectrum of reactivity, generating advanced lipoxidation end-products (ALEs) by covalent modification of proteins and relative structural and functional changes, protein aggregation, enzyme inhibition, and subcellular protein localization; DNA lipoxidative damage with potential mutagenic and carcinogenic effects and activation of signalling pathways (*i.e.*, inflammatory and anti-oxidant responses); modification of amino-phospholipids and hindered membrane integrity [86]. Specifically, in the SNpc, 4-HNE has been shown to affect the dopaminergic pathway at multiple levels by modifying VMAT2 and preventing the neurotransmitter sorting into the vesicles by binding to the dopamine transporter (DAT), thus altering DA re-uptake and binding to the DA receptors D1 and D5 [80]. In addition, general modification of proteins by 4-HNE is associated with the accumulation of ubiquitinated proteins and impairment of the ubiquitin-proteasome system, activation of the apoptotic cascade, and further neurodegeneration [87, 88].

The thick arrows highlight the altered expression and/or activity of key enzymes due to ageing (magenta), genetic variants (yellow), and exposure to xenobiotics (green).

Importantly, also lipid peroxidation products are known to covalently modify aSyn and trigger its aggregation in various *in vitro*, cellular, and *in vivo* models. This has been described for acrolein [76], 4-HNE, and 4-ONE [89-94]. Of note, 4-HNE-induced aSyn aggregates display a curved proto-fibrillar morphology with β-sheet structures. Although small amounts of 4-HNE have been reported to trigger aSyn oligomerization, the principal modification site by 4-HNE is the sole histidine residue on aSyn sequence (H50), suggesting a different reactivity and aggregation kinetics compared to DOPAL modification, which occurs at several aSyn lysines.

2.3. Hyperglycemia and Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is characterized by chronic hyperglycaemia. It affects approximately 9% of the global population over 40 years old, with increased incidence in Asian populations [95]. Under pathological conditions, the increased glucose concentration in the bloodstream and tissues promotes the formation of the glycolytic sub-product MGO and the accumulation of the advanced glycating end-products (AGEs) leading to diabetic nephropathy, retinopathy, and neuropathy. Of note, the correlation between T2DM and PD is gaining attention, as patients with T2DM have an estimated 40% increased risk to develop PD [96-98].

During glucose metabolism, MGO is produced by the spontaneous degradation of glyceraldehyde-3-phosphate and dihydroxyacetone-phosphate. MGO is then primarily metabolized to D-lactate by a two-steps reaction involving the Glyoxase 1 (Glo-1) and Glyoxase 2 (Glo-2) enzymes and GSH molecules [99]. However, the observed age-dependent decreased Glo-1 expression and depletion of GSH reservoir correlate with the progressive accumulation of MGO and AGEs [100-102].

In PD, the local accumulation of MGO may be further amplified by the high energy demand of the dopaminergic neurons of SNpc, which leads to an enhanced rate of glycolysis and mismatched glyoxalase system capacity [103]. Additionally, aberrant levels of the toxic aldehydes DOPAL and 4-HNE have been reported to modify and inhibit the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) covalently, thus synergistically promoting the glyceraldehyde-3-phosphate conversion to MGO [104, 105].

In addition to the Glo-1/2 pathway, a detoxifying mechanism implies a direct conversion of MGO to pyruvate by the ALDHs [106]. It follows that the reported impaired ALDH efficiency in PD hinders this compensatory mechanism from buffering MGO. Indeed, a positive correlation between diabetic complications and ALDH2 polymorphisms has been reported, particularly in Asian populations [107, 108]. Furthermore, MGO itself has been demonstrated to inhibit ALDHs at concentrations associated with pathology [106].

2.3.1. Methylglyoxal Neurotoxicity

MGO physiological concentration in the plasma is about 150nM. However, in T2DM, it is known to increase up to 2-6 fold [109]. MGO aldehyde moiety is highly reactive towards cysteines, arginines, and lysines of proteins in the blood and the extra-cellular matrix, leading to AGEs accumulation. Also, MGO was showed to diffuse in cells and tissue, permeating the plasma membrane [110], where it is known to alter the cellular proteome, trigger mutagenic and apoptotic processes by nucleotide glycation (mainly deoxyguanosine), and affect membrane bilayer integrity by lipid glycation [99].

Increased amounts of AGEs in the brains of patients with synucleinopathies has been widely recognized, specifically in SNpc and LC of PD subjects [15, 16]. Once again, aSyn appears to be the preferential target of MGO covalent modification. Indeed, the MGO-induced aSyn aggregation and altered clearance were proved in cellular systems as well as *in vivo* mouse and fly models, together with the impairment of the autophagy-lysosomal pathway and general neurotoxic outcomes [111].

In (Fig. **2**), the potential pathological mechanisms that generate increasing concentrations of biogenic aldehydes in the degenerating neurons in PD are represented, together with the mechanisms of aldehyde-associated neurotoxicity.

3. CLINICAL AND PRE-CLINICAL DRUGS WITH ALDEHYDE SCAVENGING PROPERTY AS THERAPEUTIC STRATEGY IN PARKINSON'S DISEASE

Based on the evidence reported above and on the complex network of intersecting pathways described (Fig. **2**), what emerges is the need for effective and specific interventions to counteract the heavy burden of reactive aldehydes in the brain. Besides targeting the single steps in the metabolic processes, the use of small molecules as scavengers to remove the excess of biogenic aldehydes appears of interest.

Here, we will focus on drugs that have been investigated for the treatment of PD and other diseases but have also been found, both at the clinical and pre-clinical stage, to possess secondary aldehyde scavenging properties (Table **1**). Among them, the anti-glycating agents, such as metformin, aminoguanidine, and pyridoxamine, were investigated and used as therapeutic strategies in diabetes and related conditions. Drugs like hydralazine, ambroxol, and rasagiline that are used in the therapy for hypertensive disorders, bronchopulmonary diseases, and idiopathic PD, respectively, showed secondary aldehyde scavenging activity through the primary amino group in their chemical structure. Similarly, the food supplements thiamine and carnosine were reported to possess aldehyde scavenging properties.

The rationale is based on the capacity of primary amines (*i.e.*, aminoguanidine, pyridoxamine, ambroxol, aminoidan, thiamine, carnosine) and hydrazine groups (*i.e.*, metformin, hydralazine) to covalently react with the aldehyde moiety and form unreactive and hydrophilic reaction products (with high clearance). Several chemical reactions and multistep processes are usually involved, mainly through Schiff base formation with the generation of immine (Fig. **3a**) and hydrazine (Fig. **3b**) derivatives, following Michael addiction, condensation, or substitution.

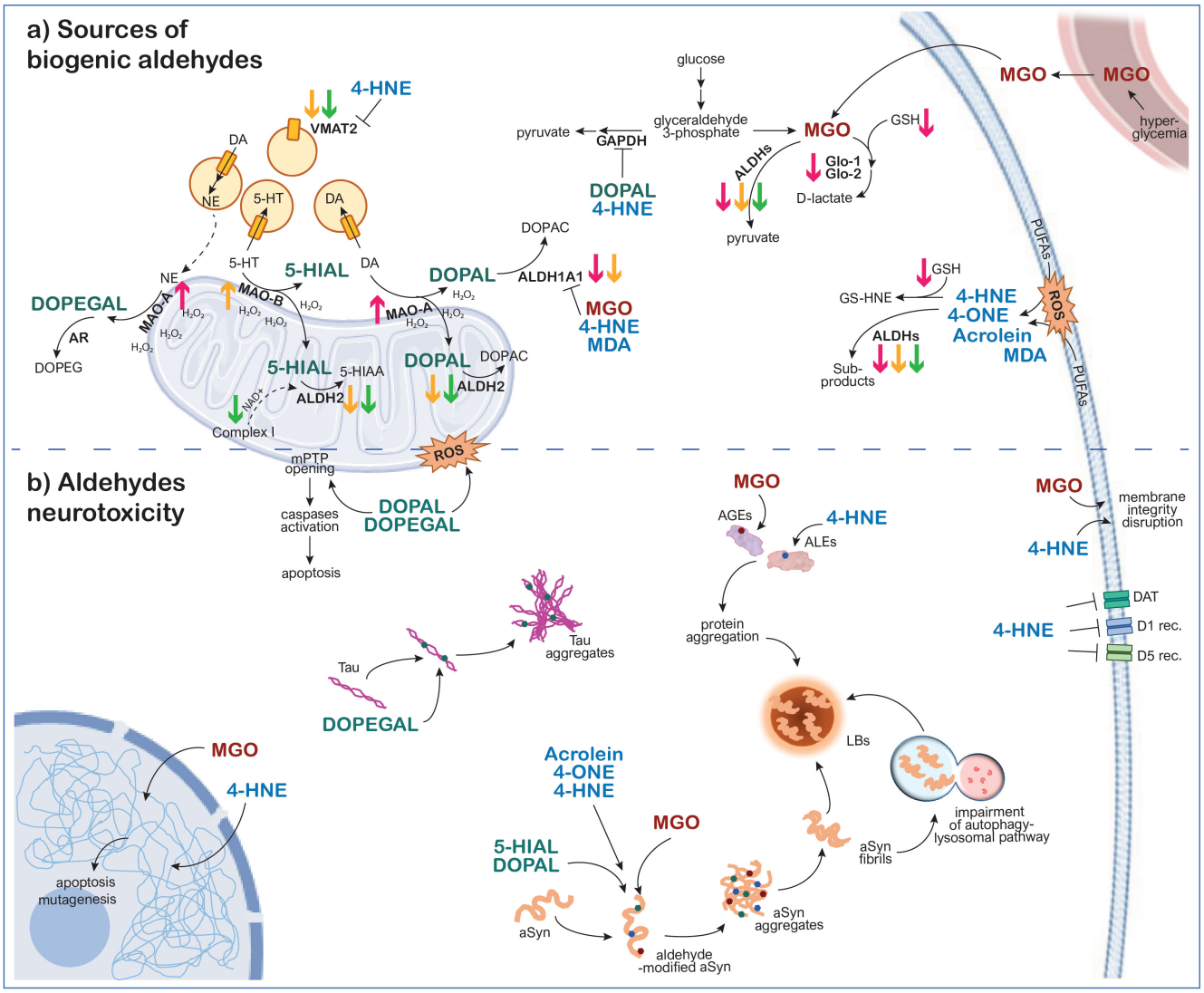


Fig. (2). Cellular pathways lead to (**a**) biogenic aldehydes build-up and (**b**) aldehyde-associated neurotoxicity in neurons of SNpc, LC, and DRN in PD. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

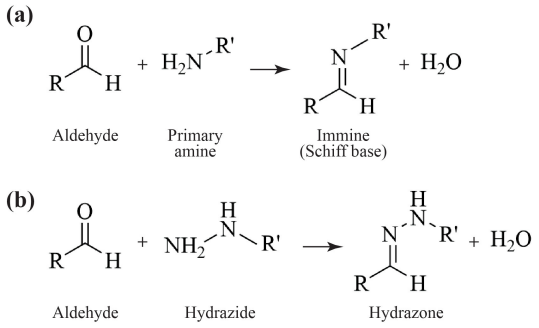


Fig. (3). Schiff-base reactions between the aldehyde and the scavenging groups in the proposed drugs. (**a**) The chemical reaction between the aldehyde and the primary amine generates an immine. (**b**) The chemical reaction between the aldehyde and the hydrazide produces hydrazine.

Table 1. Chemical structures of clinical and pre-clinical drugs and food supplements with aldehyde scavenging property.

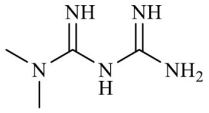
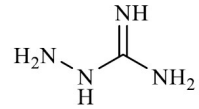
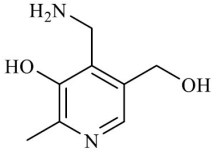
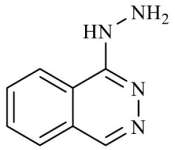
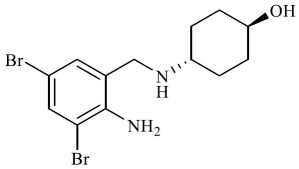
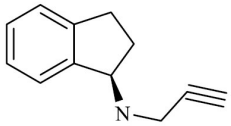
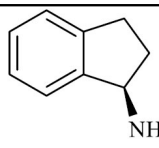
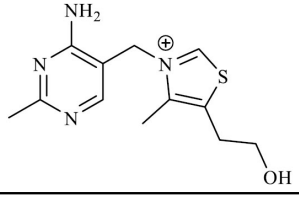
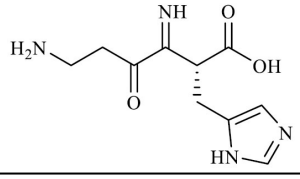
Drug	Chemical Structure
Anti-glycating agents	
Metformin *(N, N-dimethylbiguanidine)*	
Aminoguanidine *(2-aminoguanidine)*	
Pyridoxamine *(4-(amidomethyl)-5-(hydroxymethyl)-2-methylpyridin-3-ol)*	
Drugs with secondary aldehyde scavenging activity	
Hydralazine *(phthalazine-1-ylhydrazine)*	
Ambroxol *(4-[(2-amino-3,5-dibromophenyl) methylamino] cyclohean-1-ol)*	
Rasagiline *((1R)-N-prop-2-ynyl-2,3. dihydro-1H-inden-1-amine)*	
Aminoidan *(1-indanamine)*	
Food supplements with aldehyde scavenging properties	
Thiamine *(2-[3-[(4-amino-2-methylpyrimidin-5-yl) methyl]-4-methyl-1,3-thiazol-3-ium-5-yl] ethanol)*	
Carnosine *((2S) -2-(3-aminopropanoylamino) -3-(1H-imidazol-5-yl) propanoic acid)*	

Table 2. Pharmacokinetics and safety data of clinical and pre-clinical drugs with aldehyde scavenging property.

Drug	Dosage* and Administration	Bioavailability	BBB Passage	Metabolism	Half-Life	Elimination Route	Potential Side-Effects	FDA Approval	Refs.
Metformin	500-1700 mg/-day in oral form	40–60%	Yes	None, no hepatic metabolism	About 5 hours	Urine (90%), unchanged	GI irritation, lactic acidosis, hypoglycemia, decreased vitamin B12 absorption	In 1995, for T2DM therapy	[113, 114, 116, 118, 183]
Aminoguanidine	300-600 mg/-day in oral form	5% (rapid renal elimination)	Yes	Metabolized in the liver in 2-acetylaminoguanidine (4%)	About 4 hours	Urine, mostly unchanged	iNOS inhibition, altered immunological responses, vascular and respiratory deficits	Withdrawn in Phase III clinical trial (1999)	[126, 127, 131, 184, 185]
Pyridoxamine	100-600 mg/-day in oral form	65%	Yes	Partially metabolized to active forms pyridoxal phosphate and pyridoxamine phosphate	1.5 hours (in rats)	Urine as 4-pyridoxic acid	Well tolerated	In Phase III clinical trial in T2DM patients	[134, 186-189]
Hydralazine	20-40 mg by IV injection emergently; 40-200 mg/day in oral form	16–35% Depending on patient's acetylator phenotype	Yes	Significantly metabolized in the liver by acetylation; Phthalazine and pyruvic acid hydrazone (inactive metabolite) are main metabolites	3-7 hours, depending on patient's acetylator phenotype	Urine (65-90%); faeces (<10%); both unchanged and as metabolites	Headache, palpitations, GI irritation, vomiting, lupus-like syndrome, hypotension	In 1997, to treat hypertensive disorders	[146, 149, 190, 191]
Ambroxol	525 - 1260 mg/-day in oral form (PD clinical trials doses)	About 80%	Yes	Metabolized in the liver to di-bromoanthranilic acid and glucuronide forms	About 10 hours	Urine (85%) mostly as metabolites	Skin rashes, GI complaints, low risk of anaphylaxis	In 1979, used for respiratory diseases; in Phase II clinical trial for PD	[160, 165, 168, 169, 192, 193]
Rasagiline	0.5-1 mg/day in oral form; 1,25 mg/day by transdermal patch	About 36%	Yes	Hepatic, 1-aminoindan (major metabolite), 3-hydroxy-N-propargyl-1-aminoindan, and 3-hydroxy-1-aminoindan	1.5–3.5 hours	Primarily *via* urine (62%) and secondarily *via* feces (7%), only 1% were excreted unchanged	Headache, dizziness, insomnia	In 2006, for PD therapy	[194-196]
Thiamine	5-300 mg/day by injection or in oral form	3.7-5.3%	Yes	Acid metabolites (2-methyl-4-amino-5-pyrimidine carboxylic acid, 4-methyl-thiazole-5-acetic acid, and thiamine acetic acid	3-5 hours	Urine, but applies only for the unphosphorylated and the acidic metabolite forms	Well tolerated, some allergic reactions and skin irritation	Approved as food supplement	[137, 175, 176, 181, 197-200]
Carnosine	50-2000 mg/-day in oral form	Low, instable due to serum carnosinase	Yes	Entry in the blood stream mostly unchanged, serum carnosinase hydrolyzes it into β-alanine and L-histidine	Specific half-life of carnosine has not been established in humans	Urine, mostly as β-alanine and L-histidine, hydrolyzed also in the kidney	No side effects reported	No	[201-203]

*The reported dosages were noted by clinical practice or by relevant clinical trials.

Drugs of this kind are of great interest, being that the pharmacodynamics, pharmacokinetics, and safety profile (see Table **2** for details) have already been assessed, and these could be included, as combination therapy, in regimens of PD patients.

3.1. Anti-glycating Agents

3.1.1. Metformin

Metformin hydrochloride (1,1-dimethylbiguanide) is a biguanidine molecule and anti-hyperglycemic agent derived from galegine, a natural product from the plant *Galega officinalis*.

Approved by FDA in 1995, metformin (known under the trade name Glucophage, among others) is still considered the first-line therapy for the treatment of T2DM [112]. Indeed, the most important benefits of metformin are associated with the regulation of glucose metabolism in diabetes-related conditions as it reduces hepatic gluconeogenesis, increases insulin sensitivity, and promotes peripheral glucose uptake [113].

At a molecular level, multiple mechanisms of action have been proposed, at times multifaceted and not fully clarified. The anti-hyperglycemic effect of metformin is supposed to be mediated by both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. It is

also known to affect both the mitochondrial and lysosomal physiology by inhibiting the complex I of the respiratory chain and the glycerophosphate dehydrogenase and by modulating the mTOR signalling pathway [114].

In addition to the modes of action mentioned above, metformin displays a therapeutic effect as an aldehyde scavenger through the guanidino group and the primary amine in its structure. Specifically, it has been demonstrated to act as an anti-glycating agent by lowering the levels of circulating dicarbonyls, covalently binding to MGO, and producing inactive imidazolinone compounds that are secreted in the urine [115, 116]. Hence, metformin not only actively regulates the glucose homeostasis in diabetic patients but also protects from associated complications by reducing systemic AGEs and MGO-protein adducts.

Interestingly, the therapeutic potential of metformin in age-related diseases is increasingly discussed. The rationale relies on the positive correlation reported between the incidence of diabetes and neurodegenerative diseases [96-98]. Secondly, metformin acts on molecular mechanisms that are usually involved in degenerative processes, *i.e.*, signalling pathways related to glucose metabolism, oxidative stress, proteostasis, and inflammation [117]. These mechanisms are all relevant for PD, and coherently, cellular and animal models have been used to demonstrate the neuroprotective effects of metformin, as extensively reviewed in Paudel *et al*. [118]. Briefly, metformin has been shown to improve motor performance and ameliorate the cognitive functions of MPTP rodent models of PD, as well as reducing their dopaminergic neuron loss in the SNpc [119]. The latter seems to depend on the regulating effect of metformin on mitochondrial functions and on reducing the ROS production and oxidative stress. Furthermore, both the autophagy induction, which promotes the clearance of misfolded and aggregated proteins like aSyn, and the decreased phosphorylation at serine 129 (a pathological signature of aSyn), are also related to the metformin action on the mTOR-dependent pathway [120, 121].

Despite these promising indications from the pre-clinical phase, clinical studies of metformin administration to PD patients provided conflicting results. When used in a Taiwanese population cohort in combination with sulfonylurea, another anti-hyperglycaemic agent, metformin counteracted the increased risk of PD in T2DM patients treated with sulfonylurea alone (without providing robust evidence of a neuroprotective role of metformin *per se*) [122]. Conversely, other studies correlated the use of metformin with PD, dementia, and cognitive decline in T2DM patients in Taiwan and Australia [123, 124]. However, these discrepancies might derive from the differences in the study designs, populations involved, diagnostic criteria, dose, and duration of metformin treatments. More recently, a large longitudinal study (5528 patients in total, with a median follow-up of 5.2 years) on US elderly veterans (mean age 63.2±10.9 years) with T2DM demonstrated that long-term metformin administration (more than 4 years) was associated with significantly decreased risk (HR 0.19, 95% CI 0.12 to 0.31) of both PD and AD [125], opening again for future interests in unravelling the therapeutic relevance of metformin in neurodegenerative diseases.

3.1.2. Aminoguanidine

Analogous to metformin in structure, aminoguanidine hydrochloride is a synthetic drug with nucleophilic hydrazine ($-NHNH_2$) and a guanidine ($-NHC(=NH)NH_2$) group. Although it was first synthesized more than a century ago, the translational potential of aminoguanidine emerged in the 90' when it was proposed as an investigational drug for the treatment of diabetic nephropathy and retinopathy under the trade name of Pimagedine.

Because of its molecular structure, aminoguanidine is an effective scavenger of α,β-dicarbonyl glycating agents, both *in vitro* and *in vivo* experimental models. The reaction between aminoguanidine and MGO generates non-toxic compounds and prevents the formation of AGEs, whose accumulation is frequently associated with secondary complications in diabetic patients [126, 127]. In addition, besides the preferential reactivity towards MGO, aminoguanidine was also shown to act as scavengers of aldehydes derived from lipid peroxidation, preventing the amino acid and protein modification by 4-HNE and MDA *in vitro* experiments [128, 129].

Of note, the therapeutic potential of aminoguanidine as an anti-glycating drug has also been investigated in neurodegenerative diseases. For instance, aminoguanidine administration to an AD mouse model with and age-dependent inhibition of β-amyloid glycation significantly reduced the cognitive deficits, Tau hyperphosphorylation, and loss of synaptic elements in the Tg2576 mouse model of AD [130]. More recently, the treatment with aminoguanidine rescued the MGO-induced aggregation and impaired clearance of aSyn in cellular models, as well as the motor impairment in aSyn-overexpressing Drosophila, thus suggesting the aminoguanidine therapeutic potential in PD [111].

Unfortunately, when tested in the ACTION I and ACTION II clinical trials to prevent the development of nephropathy in T1DM and T2DM patients, some safety concerns and apparent lack of efficacy led to the decision to discontinue the aminoguanidine Phase III trial in '98-99 [131]. Indeed, aminoguanidine was also proved to inhibit the inducible nitric oxide synthase (iNOS) and diamine oxidase (DAO), potentially leading to aberrant immunological responses due to altered NO signalling pathway and severe vascular and respiratory deficits due to histamine accumulation in the blood, respectively [126]. Also, the molecule was well-absorbed but rapidly cleared by glomerular filtration, resulting in a bioavailability of only 5% [132]. Hence, a high dosage of aminoguanidine might be necessary, with the off-targets and side effects coming along.

On this ground, the clinical use of aminoguanidine as an aldehyde scavenger will first require the development of aminoguanidine derivatives to improve its bioavailability, as well as prodrug formulations to be activated in the regions of interest, thus improving the therapeutic odds of aminoguanidine in both T2DM and PD.

3.1.3. Pyridoxamine

Pyridoxamine, a naturally occurring metabolite and a structural analog of vitamin B6 (pyridoxine), has been developed as a broadly active inhibitor in the early and late stages of AGEs formation. It is currently under phase III clinical trial to determine its efficacy in reducing the rate of progression of nephropathy in T2DM patients [133, 134].

Interestingly, the molecule has multiple beneficial effects that are carried out by two functional groups, the hydroxyl and the aminomethyl group [135]. Among the effects is the inhibition of AGEs and ALEs formation by scavenging reactive carbonyl species [134, 136, 137], the sequestration of catalytic metal ions [138], the blockage of oxidative degradation of Amadori intermediates derived from glycated proteins [139], ROS and free radicals scavenging [140].

Although less effective than other molecules (*i.e.*, hydralazine, aminoguanidine, and carnosine) as a scavenger of biogenic aldehydes, pyridoxamine was showed to react with 4-HNE, MGO and more efficiently with MDA by producing an *N*-propenal–pyridoxamine adduct [129], as already described in previous *in vitro* studies [141] and a mouse model of diabetes [142]. Also, the neuroprotective action of pyridoxamine was explored in the rotenone-exposed mouse model of PD, where it reduced neuronal cell death associated with microglial AGE-albumin, the most abundant AGE product in the human PD brain [143]. However, to date, limited investigation of pyridoxamine beneficial role in PD therapy is conducted, although a high (2.3-5.6 mg/day) dietary intake of vitamin B6 (pyridoxine) has been associated with a decreased risk of PD [144]. Conversely, a low intake of vitamin B6 is positively correlated with PD development [145]. Here, the neuroprotection by pyridoxamine can be related to its antioxidant properties and the regulation of homocysteine levels in the blood, but also its activity as aldehyde scavengers should be considered and further unraveled.

3.2. Drugs with Secondary Aldehyde Scavenging Activity

3.2.1. Hydralazine

Hydralazine hydrochloride (1-Phthalazinylhydrazine) is a hydrazine derivative, approved by the FDA under the trade name Apresoline (among others) for the treatment of essential hypertension and as an adjunct therapy to lower blood pressure in case of heart failure [146].

Hydralazine acts primarily as a vasodilator on smooth muscle cells of arterial vessels and arterioles, reducing peripheral resistance and lowering blood pressure. Although the molecular mechanisms of action are not completely understood yet, studies on animal models suggested that hydralazine might act by modulating the effect of purine-like compounds released from sympathetic nerve endings and by altering intracellular calcium release, thus interfering with smooth muscle cell calcium influx [147-149].

Since its discovery, additional studies have pointed out that hydralazine can act as a scavenger of biogenic aldehydes through its nucleophilic hydrazine moiety, which binds to free and protein-bound aldehydes to form stable hydrazones [129, 150, 151]. Its scavenging activity was shown both in cellular and animal models to be aimed mainly towards lipid peroxidation products, *i.e.*, acrolein, MDA, and 4-HNE, exerting cytoprotective effects from free aldehydes and aldehyde-protein adducts [150, 152-154]. In addition, hydralazine was shown to be effective in reducing the formation of AGEs in plasma and kidney in a mouse model of T1DM [155].

Interestingly, the therapeutic potential of hydralazine for PD was studied in different toxin-based animal and cell models. Ambaw *et al*. demonstrated that hydralazine acted as an effective scavenger of acrolein generated by lipid peroxidation, in turn, induced by injection of 6-OHDA and rotenone in rat striatum. Furthermore, it also alleviated the aggregation of aSyn, neuronal cell death, and motor deficits [76]. Guo *et al*. documented that hydralazine confers protection in dopaminergic neurons in a MPTP model of PD, alleviating oxidative stress, and activating the NRF2 pathway [156, 157]. However, reported side effects of hydralazine should be considered in the case of a purported prolonged therapy in PD patients, like immunological reaction and lupus-like syndrome [158]. Also, hydralazine has been shown to act as a weak MAO inhibitor; hence it needs to be used carefully in patients concomitantly taking other MAO inhibitors to avoid a synergistic action and severe blood pressure decrease [159].

3.2.2. Ambroxol

Ambroxol hydrochloride (*trans*-4-((2-Amino-3,5-dibromobenzyl) amine) cyclohexanol) belongs to the class of organic compounds known as phenylethylamines. It is an active and synthetic derivative of vasicine, a quinazoline alkaloid extracted from the plant *Adhatoda vasica*.

In clinical practice, it is frequently used as an expectorant and mucolytic agent to treat bronchial asthma and chronic bronchitis [160]. Indeed, the main molecular mechanisms ascribed to ambroxol are related to mucokinetic properties, mucociliary activity, stimulation of surfactant production by type II pneumocytes, anti-inflammatory, and antioxidative actions, and the local anesthetic effect [160].

Besides, ambroxol exhibited protective action against free radical species and lipid peroxidation products, *i.e.*, MDA [161-163]. Although the role of ambroxol as a direct scavenger of biogenic aldehydes has not been tested *in vitro* and *in vivo* yet, the data showing decreased lipid peroxidation and MDA levels are in line with this hypothesis. Action due to the presence of a primary amine in its structure allowed a Schiff-base reaction with reactive aldehydes.

Recently, ambroxol has gained importance as a potential therapy to slow down the neurodegeneration in PD and PD dementia (PDD), particularly in patients carrying mutations of lysosomal enzyme β-Glucocerebrosidase (GCase; gene name GBA1). First, the use of ambroxol in cell culture and animal models of PD resulted in reduced aSyn aggregation levels. Second, it acted as a pharmacological chaperone to in-

crease the activity of GCase [164-167]. From this evidence and due to the excellent safety profile of this drug, two clinical trials were conducted (*Clinical.gov*: NCT02914366, NCT02941822) in PD patients with and without GBA1 mutations, confirming the ambroxol as a promising therapeutic approach for PD [168, 169].

3.2.3. Rasagiline

Rasagiline (N-propargyl-1(R)-aminoidan) is a selective and irreversible inhibitor of MAO-B and has been used in the therapy of PD since its EMA and FDA approval in 2005-2006.

The rationale is to elevate the dopamine levels by preventing its deamination by MAO in the first catabolic step, thus sustaining the activity of dopaminergic neurons and improving the motor symptoms.

Aside from the MAO activity inhibition, extensive literature now supports a more general neuroprotective action of rasagiline in several experimental models of PD [170]. The drug has been demonstrated to prevent neuron death through many molecular mechanisms, *i.e.*, by acting as an antioxidant molecule, by inducing the gene expression of neurotrophic factors, antioxidant and anti-apoptotic enzymes, and by regulating mitochondrial physiology.

Moreover, rasagiline has been shown to interfere with aSyn aggregation through at least three mechanisms. First, rasagiline and its major metabolite R-1-aminoidan (produced by cytochrome P450-1A2 in the liver) were shown to interact with the N- and C-terminal regions of aSyn, forming a less-prone-to-aggregation loop structure [171]. Second, by blocking the formation of the monoamine-derived aldehydes DOPAL and 5-HIAL, rasagiline administration prevents the aldehyde-induced aSyn modification and aggregation [70, 71]. Finally, both rasagiline and R-1-aminoidan appeared to act as DOPAL scavenger through a Schiff-base reaction between the aldehyde and the amino group in the drugs' structure, thus preventing aSyn aggregation and reducing DOPAL-induced toxicity in PC-12 cells [172].

Despite the many beneficial effects ascribed to rasagiline therapy in PD, the drug demonstrated disease modification at the dose of 1 mg but not at 2 mg, possibly because of inadequate study design and patients' stratification [173, 174].

3.3. Food Supplements with Aldehyde Scavenging Properties

3.3.1. Thiamine

Thiamine hydrochloride, also known as vitamin B1, is an essential cofactor in several metabolic processes, such as glucose metabolism and cellular energy handling. This water-soluble vitamin is not endogenously produced in the human body; therefore, it must be taken with the diet. It is mostly found in leafy green vegetables, eggs, grain, and meats [175]. Hence, thiamine pharmaceutical supplementation is primarily used to treat and prevent its deficiency or related disorders, including Beriberi and Wernicke–Korsakoff syndromes.

In addition to its metabolic cofactor activity, thiamine was reported to exert a protective role against lipid peroxidation products in rat liver and kidney [176]. *In vitro* experiments also proved the thiamine pyrophosphate scavenging activity for AGEs [137], further confirmed in endothelial cellular models exposed to high glucose concentrations [177] and rodent models of diabetes [178]. Importantly, thiamine was shown to reduce circulating glucose levels when administered to hyperglycaemic patients [179]. Hence, these preliminary data and the presence of a primary amine in the molecular structure suggest a promising action of thiamine as an aldehyde scavenger, whose characterization should be extended to PD models.

In the last years, several studies pointed out a possible interplay between thiamine levels and PD [180, 181], where low plasma concentration of vitamin B1 was associated with mild cognitive decline in PD patients [182].

3.3.2. Carnosine

Carnosine is an endogenous histidyl dipeptide, consisting of a β-alanine bound to histidine. It is abundantly synthesized by the Carnosine Synthase 1 (CRNS1 or ATPGD1) in skeletal muscles and other tissues such as the brain, heart, spleen, and kidney [204], but it is also available as an oral drug and food supplement.

Endogenous carnosine displays a variety of defensive effects by exhibiting pH buffering capacity, metal chelating activity, and antioxidant properties. More interestingly, carnosine has been proved to act as an aldehyde scavenger, as demonstrated by several *in vitro* and *in vivo* studies [201, 202].

Carnosine has proven to prevent MGO protein modification and AGEs formation through different mechanisms, *i.e.*, by a trans-glycating effect and by removing the glucosyl-adduct from proteins [205, 206]; directly quenching reactive carbonyl species (RCS) [129]; by inhibiting the metal-catalyzed oxidative conversion of glycated proteins to AGEs [207]. Also, carnosine is known to inhibit ALEs formation by reacting with α,β-unsaturated aldehydes, and forming covalent adducts that are excreted in the urine [208, 209]. Chemically, the detoxification occurs by a multistep reaction where both the amino group of β-alanine and the imidazole ring act synergistically to form the stable hemiacetal derivative [129]. For example, its quenching activity towards 4-HNE was showed both *in vitro* [129] and *in vivo* [210], demonstrating that dietary supplementation of carnosine could attenuate the development of dyslipidemia, hypertension, and carbonyl stress in rodent models of obesity and atherosclerosis [209, 211].

Of note, Nelson *et al*. recently demonstrated that DOPAL and DOPEGAL could be scavenged by carnosine, demonstrating the therapeutic potential of carnosine in diseases associated with catecholamine-related toxicity [212].

Interestingly, carnosine pre-treatment appeared to prevent neurodegeneration and apoptosis activation in 6-OHDA-injected rats [213]; to exert antioxidative and anti-inflammatory protection in the striatum of MPTP-treated mice

[214]; to restore the normal antioxidant activity and physiological DA and 5-HT monoamine metabolism in MPTP-exposed rats [215]. Also, the group of Genter provided evidence that daily intranasal administration of carnosine had a positive impact on mitochondrial function and a protective role in preventing the progression of PD symptoms, motor deficits, and aSyn aggregation in the Thy-1 aSyn genetic mouse model [216, 217].

To date, one clinical trial investigated the efficacy of carnosine (1.5 g/day) in PD patients in combination with L-Dopa therapy [218], where a significantly increased efficacy of the L-DOPA treatment and improvements in clinical symptomatology were reported. Also, initiating in 2017, another PD clinical trial aimed to investigate the beneficial effects of exercise training and carnosine dietary supplementation on cognitive, motor, and metabolic functions have been reported (NCT03330470).

4. ALDEHYDE SCAVENGING THERAPY IN PARKINSON'S DISEASE: GENERAL CONSIDERATIONS

Since PD has multi-systemic and multifactorial pathology, the idea of simultaneously targeting multiple affected processes could be a promising therapeutic strategy [219]. On this basis, the previously mentioned drugs support this concept since, in addition to their aldehyde scavenging activity, they display multiple modes of action, targeting various molecular mechanisms associated with PD.

Molecules like metformin and ambroxol would scavenge toxic aldehydes in the brain and also activate protein clearance and lysosomal activity to avoid the accumulation of protein aggregates. Hydralazine, metformin, and aminoguanidine could prevent the burden of AGEs and ALEs derived by diabetic conditions or oxidative stress generated by long-term use of L-DOPA and other antiparkinsonian medications. Rasagiline would decrease DA catabolism in dopaminergic neurons and buffer any toxic aldehyde in the cellular environment. Food supplements like thiamine, carnosine, and pyridoxamine would respond to the metabolic imbalance in certain PD patients as well as scavenge excessive biogenic aldehydes. Hence, the administration of aldehyde scavengers in conjunction with the approved symptomatic therapies might assist in developing effective strategies, possibly towards disease-modifying actions.

These approaches would indeed require a careful evaluation of the clinical outcomes following long-term use. Dose and duration adjustment, the accurate analysis of potential side effects, and the metabolic fate of the aldehyde-scavenger reaction products should be examined in future experimental research. Also, while planning new clinical trials, two important factors should not be underestimated: the timing for starting the treatment and the selection of defined patient cohorts for whom the aldehyde scavenging therapy would prove most beneficial.

Usually, once the patient's clinical picture presents a definite PD diagnosis, the neurodegeneration process would have already irreversibly expanded, making efforts at targeting pathogenic mechanisms unlikely to produce any radical changes to the course of the disease [220]. Thus, intervention in the early prodromal phases appears critical to achieving substantial disease modification. Furthermore, identifying small subgroups with a homogeneous pathophysiological basis would be necessary to accurately assess the positive outcomes from the proposed therapeutic approach [219, 220]. Therefore, it is necessary to define precise criteria for patients stratification to identify those subjects in the early stages of PD who have a higher vulnerability to excessive biogenic aldehyde yield.

According to the literature reviewed in this article, a promising strategy would comprise analysing genetic variations that were described to affect the activity of enzymes involved in the monoamines metabolism and the detoxification of aldehydes. Of note, the single nucleotide polymorphisms (SNPs) listed in Table (**3**) have also been associated, in epidemiological studies, with an increased risk to develop PD.

As a first step toward patients stratification, the analysis of these variants can be introduced in the genetic panels currently used for PD, thus facilitating the early identification of patients at risk for aldehyde-related pathology. Here, the first candidates for genetic screening of these SNPs could be those who display early signs of prodromal symptoms of PD, like REM Behaviour Disturbances (RBD). Indeed, dysfunction in the serotoninergic system contributes heavily to both motor and non-motor symptoms of PD [221], and the accumulation of serotonin-derived aldehyde supposedly contributes to sleep disturbances. For instance, a recent study involving 83 idiopathic PD patients in Taiwan highlighted the increased difficulty in sleep maintenance in patients carrying the A allele in the rs671 SNPs of the *Aldh2* gene, which encodes for an enzyme with significantly reduced enzyme activity [48]. It is worth mentioning that the rs671 genetic variant is highly frequent in Asian populations, where the genetic interchange has been limited compared to those from

Table 3. List of SNPs in genes encoding enzymes involved in monoamines metabolism and aldehyde degradation that have been associated with increased risk to develop PD.

Gene	Genetic Variations
Vmat2	rs363371 and rs363324 [25]; rs1392638187 [26];
Mao-b	rs1137070 and rs1799836 [36]; rs1799836 [35];
Aldh1a1	rs3764435 [46];
Aldh2	Haplotype rs737280, rs968529, rs16941667, rs16941669, rs9971942 [43]; haplotype rs4767944, rs441, rs671 [44]; rs671 [45, 47, 48, 222].

Europe and America. Moreover, to our knowledge, the work by Lin *et al*. is the first study associated with sleep disturbances with impaired aldehyde metabolism. Further comprehensive investigations on RBD patients would accordingly be required, assessing larger cohorts reflective of populations with diverse genetic backgrounds. This approach should enhance the genetic stratification of patients to test the efficacy of an aldehyde scavenging-based therapy.

In addition to genetic screening, the development and assessment of specific biomarkers of biogenic aldehyde build-up would reinforce the criteria for identifying the best candidates. The updated list of cerebrospinal fluid (CSF) and blood biomarkers includes read-outs of well-established pathological elements, *i.e.*, the presence of aggregated proteins like aSyn, Tau, and amyloid-beta, the activity of lysosomal enzymes, and neurofilament light chain levels [223]. However, other studies investigated the diagnostic potential of elevated aldehyde concentrations in biological fluids. For instance, in a study conducted in West Bengal in 2009, a significantly increased MDA concentration in the plasma of PD patients was estimated compared to the healthy subjects (7.48 ± 1.55 nmol/ml *vs.* 5.10 ± 1.26 nmol/ml) [78]. More recently, the analysis of various biomarkers of immuno-inflammation and ROS in PD patients from a Brazilian cohort revealed the quantification of MDA in the peripheral blood as the most sensitive and specific biomarker for PD. It accordingly described increasing MDA levels in early PD (201.9 ± 18.9 μM/mg of proteins) and late PD (214.1 ± 29.7 μM/mg of proteins) subjects compared to healthy controls (168.1 ± 18.3 μM/mg of proteins) [79].

Furthermore, there have been investigations on the read-outs of an altered dopamine metabolic pathway. In a study, the analysis of dopamine and its metabolites in the CSF of patients with PD and parkinsonian multiple system atrophy (MSA-P) demonstrated a correlation between the pathology and the decreased concentration of DOPAC (1.60 ± 0.12 pmol/ml in healthy control *vs.* 0.94 ± 0.09 pmol/ml in PD patients and 0.89 ± 0.08 pmol/ml in MSA patients) [224]. Together with a decreased DOPAC/DA ratio and increased 5-S-Cysteinyl-dopamine/DOPAC ratio, this data suggested elevated oxidative stress and impaired ALDH activity in the SNpc dopaminergic neurons of parkinsonian patients, potentially leading to the accumulation of toxic aldehydes. Coherently, another metabolomic study assessed a statistically significant increase in DOPAL levels (p-value 0.000177) in PD patients' plasma compared to healthy subjects [225]. Finally, the analysis of plasma samples from PD patients from a Chinese cohort compared to healthy controls identified aSyn species specifically modified by dopamine and DOPAL on lysine residues that could only derive from diseased dopaminergic neurons in PD patients [226].

Although very promising, the plasma/CSF concentration of these biogenic aldehydes would require more comprehensive studies to confirm their robustness as a biomarker for PD. First, a large-scale collection of samples from various patient cohorts should be analysed to define thresholds that identify prospective or already established PD patients. Second, RBD patients and subjects with prodromal PD signs should be enrolled to perform longitudinal post-hoc studies and assess whether the measured aldehyde levels are consistent with the following diagnosis of PD. Accordingly, this approach may outline values to identify the heterogenous clinical phenotypes and varying disease progressions [227] to adjust the therapeutic approach further. Finally, as an additional level of complexity, the plasma and CFS aldehyde profiling ought to consider possible inconsistency due to concurrent use of vitamins and food supplements, prescribed medications (*i.e.*, Antabuse drugs, anti-glycating agents, L-DOPA), and exposure to toxins and pesticides that are known to interfere with the aldehyde metabolic pathways.

Taken together, the implementation of genetic panels with variants on *Vmat2*, *Mao-b*, *Aldh1a1*, and *Aldh2* genes and the definition of biomarkers of aldehydes and aldehyde-adducts in the CSF or peripheral blood would represent powerful diagnostic and prognostic tools. On those bases, introducing the aldehyde scavenging therapy in subjects at the earliest stages of PD may help to prevent the toxic accumulation of biogenic aldehydes and exacerbate concomitant pathological mechanisms, thus acting as neuroprotective agents and delaying the progression of the disease.

CONCLUSION

The development of successful therapeutic interventions to modify PD progression still presents a great challenge given the complexity of the pathology and the broad spectrum of clinical manifestations.

At a molecular level, several pathological mechanisms contribute to the progressive dopaminergic neuron loss, among which the excessive accumulation of biogenic aldehydes in the brain appears to play an important role. On this basis, introducing an aldehyde scavenging therapy combined with other antiparkinsonian medications would contribute to elaborating disease-modifying strategies for PD.

Accordingly, this work described a series of drugs that may prove useful because of their secondary aldehyde scavenging properties, assessed in pre-clinical studies. Ideally, it would eventually be possible to predict which aldehyde would be more prone to accumulate in a given patient and which scavenger would exploit the best neuroprotective action as a sort of personalized medicine.

Of course, a deep analysis of the pharmacology and bioavailability of the proposed drugs in the brain, as well as the potential side effects from associated long-term use, ought to be conducted. However, a drug repurposing operation for these molecules, some of which are already off-patent, would encounter several legal, regulatory, and economic barriers. Although repositioning an already approved medication should entail fewer risks, lower costs, and shorter timelines for approval, the incentives to assess a new dosage and toxicology according to the new target and to run new clinical trials are still probably insufficient [228-230].

Moreover, to unequivocally prove or disprove the efficacy of aldehyde scavenging therapy in PD, the design of clini-

cal trials in selected groups based on precise criteria for patients' stratification will be necessary. Accordingly, in the first instance, it is proposed that there be an upgrade of the genetic screening panels with variants on genes involved in aldehyde metabolic pathways. Second, subjects with prodromal symptoms of PD, *i.e.*, RBD patients, should be tested for blood biomarkers of biogenic aldehyde accumulation. Finally, it would be critical to perform studies on a larger scale, enrolling subjects representative of diverse genetic backgrounds and clinical histories to match the broad spectrum of onset, symptoms, and pathology of PD.

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CONFLICT OF INTEREST

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