

Monoamine Oxidase B in Astrocytic GABA Synthesis: A Central Mechanism in Neurodegeneration and Neuroinflammation

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Abstract

Monoamine oxidase B (MAO-B) is a mitochondrial enzyme predominantly expressed in astrocytes, where it plays a crucial role in neurotransmitter metabolism, oxidative stress regulation, and neuroinflammation. In addition to its well-characterized function in the oxidative deamination of monoamines such as dopamine, noradrenaline, and serotonin, MAO-B is increasingly recognized for its involvement in astrocytic GABA synthesis. In reactive astrocytes, upregulated MAO-B activity enhances GABA production, leading to excessive tonic inhibition that disrupts neuronal excitability and synaptic function. Moreover, MAO-B-mediated metabolism generates reactive oxygen species (ROS), including hydrogen peroxide, further exacerbating oxidative stress and neuroinflammation. This article examines the critical role of MAO-B in neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke, emphasizing its contribution to impaired GABAergic signaling and neurodegeneration. Finally, it explores the potential of MAO-B inhibition as a targeted therapeutic approach to regulate astrocytic GABA synthesis, mitigate aberrant inhibitory signaling, and restore neural circuit homeostasis in neurodegenerative and metabolic disorders.

Keywords: Monoamine oxidase B, Astrocytes, GABAergic signaling, Alzheimer's disease (AD), Parkinson's disease (PD), Stroke and CNS injury, Reactive oxygen species (ROS), Astrocytic GABA synthesis, Neural circuit, and NSCs proliferation activity

Introduction

Monoamine oxidase (MAO) is a mitochondrial enzyme responsible for the oxidative deamination of biogenic amines, including dopamine (DA), serotonin, norepinephrine, and melatonin [1,2]. Through its regulation of neurotransmitter levels, MAO plays a pivotal role in mood regulation, cognition, and motor control [3,4]. MAO exists in two isoforms, MAO-A and MAO-B, which differ in their substrate specificity, tissue distribution, and physiological functions [5,6].

MAO-A primarily metabolizes serotonin, norepinephrine, epinephrine, and melatonin and is predominantly expressed in dopaminergic axon terminals, particularly within the nigrostriatal pathway [1,2,7]. In contrast, MAO-B primarily degrades phenylethylamine and benzylamine, with a

secondary role in dopamine metabolism. Notably, MAO-B is highly expressed in astrocytes, where it contributes to neurotransmitter homeostasis in non-neuronal brain cells [8,9]. While both isoforms are capable of metabolizing dopamine, MAO-A is the principal enzyme responsible for dopamine degradation in neurons, due to the high expression of the dopamine transporter (DAT) in dopaminergic terminals. Conversely, MAO-B's role in dopamine metabolism is limited by the lack of DAT expression in astrocytes, restricting dopamine uptake in these cells [10,11].

Beyond its role in dopamine metabolism, MAO-B plays a crucial role in astrocytic GABA synthesis. In particular, reactive astrocytes modulate neuronal excitability through GABA production. MAO-B facilitates this process by metabolizing putrescine into 4-aminobutanal, which is subsequently

converted into GABA [12,13]. This pathway contributes to tonic inhibition of neuronal activity, particularly in the striatum and substantia nigra pars compacta (SNpc). Dysregulation of this process has been implicated in neurodegenerative diseases such as Parkinson's disease (PD), where reactive astrocytes increase GABA synthesis in response to neuronal injury, leading to excessive tonic inhibition and exacerbating motor deficits [14-17].

In addition to PD, MAO-B has been linked to Alzheimer's disease (AD) and stroke-related neuronal injury. In AD, elevated MAO-B expression in astrocytes is associated with increased oxidative stress, amyloid-beta aggregation, and neuroinflammation, contributing to cognitive decline [18,19]. Similarly, in ischemic stroke, increased MAO-B activity has been implicated in excitotoxicity and neuronal apoptosis, as reactive astrocytes upregulate MAO-B expression following ischemic events [9]. Consequently, inhibition of MAO-B has been proposed as a therapeutic strategy to mitigate oxidative stress, neuroinflammation, and excessive GABA-mediated tonic inhibition in neurodegenerative and ischemic disorders [20,21].

In addition to its role in astrocytes, lateral ventricle (LV) neural stem cells (NSCs) also play a significant role in GABA regulation. These cells either directly synthesize GABA or uptake it from the extracellular space [22]. Upon activation of the ACC- subependymal -ChAT⁺ (subep-ChAT⁺) circuit, which modulates the proliferative activity of LV NSCs, these cells exhibit an upregulation of both MAO-B activity and GABA production [22,23]. This suggests that LV NSCs may synthesize GABA through the MAO-B enzyme, similarly to astrocytes, given that LV NSCs exhibit glial-like behavior. The synthesized GABA is then released into the microenvironment between LV NSCs and subep-ChAT⁺ neurons. This release is thought to function as a feedback mechanism, potentially modulating the activity of the ACC-subep-ChAT⁺ circuit and influencing LV NSC proliferation [24]. Such regulatory mechanisms are essential for neurogenesis, as they help balance stem cell activity over time, allowing LV NSCs to exert control over external regulatory influences and maintain homeostasis within the neurogenic niche.

This article investigates the critical role of MAO-B in astrocytic GABA synthesis and its broader implications for neurological health and disease. It examines how MAO-B-mediated metabolism influences GABAergic signaling, particularly in reactive astrocytes, where its dysregulation contributes to excessive GABA production, neurotransmitter imbalance, and neuronal inhibition. Furthermore, the article explores the impact of MAO-B activity in neurodegenerative conditions such as AD, PD, and stroke, emphasizing the potential of MAO-B inhibition as a therapeutic approach to modulate astrocytic function, restore synaptic homeostasis, and mitigate neurodegeneration.

MAO-B in Neurophysiology and Disease: Astrocytic Role in Neurotransmitter Homeostasis, Oxidative Stress, and Therapeutic Implications

The role of MAO-B in astrocytic function, neurotransmitter regulation, and neurological disease pathophysiology

MAO-B is a mitochondrial enzyme that plays a pivotal role in maintaining neurotransmitter homeostasis through the oxidative deamination of monoamines [25,26]. Originally identified in the 1920s as tyramine oxidase in the liver, MAO-B was later reclassified to distinguish it from other oxidative deaminases. By the 1950s, its presence in the brain was established, revealing its capacity to oxidize catecholamines, including DA, adrenaline, and noradrenaline [1,27,28]. These discoveries emphasized the enzyme's critical role in neurophysiology and its broader implications for neural function and disease.

MAO-B is widely distributed in key brain regions, including the cerebral cortex, cerebellum, hippocampus, and midbrain, with its predominant localization in astrocytes. Immunohistochemical and *in situ* hybridization studies have confirmed its enrichment in astrocytes in both rodent and human brains. It is also present in serotonergic and histaminergic neurons, particularly in the dorsal raphe and tuberomammillary nucleus [29-32]. The predominant presence of MAO-B in astrocytes underscores its essential role in glial-mediated modulation of neurotransmission, regulation of neuroinflammation, and oxidative stress, all of which influence neuronal survival and synaptic function [33-35].

In addition to its role in neurotransmitter regulation, MAO-B is involved in the conversion of polyamines, such as putrescine, into gamma-aminobutyric acid (GABA), a key inhibitory neurotransmitter in the central nervous system (CNS) [17]. This process becomes especially important within reactive astrocytes—glial cells that undergo morphological and functional changes in response to persistent metabolic stress. The MAO-B-mediated synthesis of GABA establishes a critical link between lipid metabolism and neurochemical signaling in the brain, highlighting its relevance in brain function and pathology [36,37].

Astrocytes exposed to chronic levels of medium-chain fatty acids (MCFAs), such as dopamine, exhibit an increase in GABA production, which serves to inhibit neuronal activity [14,38]. This upregulation of GABA synthesis is especially pronounced in brain regions such as the hypothalamus, a central hub for regulating energy homeostasis, feeding behavior, and metabolic balance [39]. Alterations in GABAergic signaling in the hypothalamus may influence broader physiological processes, emphasizing the importance of astrocytic regulation in maintaining brain and body homeostasis [39,40].

Furthermore, MAO-B activation in astrocytes contributes to the generation of reactive oxygen species (ROS), including hydrogen peroxide (H₂O₂), which induces oxidative stress [34,41]. The accumulation of ROS exacerbates cellular dysfunction by disrupting the balance within astrocytic populations, promoting hypertrophy, proliferation, and inflammation [42]. These changes impair the supportive functions of astrocytes, further compromising neuronal integrity. The interplay between oxidative stress and metabolic reprogramming in reactive astrocytes highlights the complexity of glial responses to chronic metabolic disturbances [43].

Such disturbances are commonly observed in various neurological diseases, where the interplay between GABA synthesis, ROS production, and altered astrocytic function plays a significant role in disease progression [13,44]. These processes may not only contribute to the pathophysiology of neurological disorders but also offer potential therapeutic targets for modulating astrocytic activity and restoring metabolic homeostasis in the brain.

Gliotransmission and astrocytic GABA: Implications for brain homeostasis and neurological disorders

Recent advancements in gliotransmission have revolutionized our understanding of astrocytes, which were once viewed as passive support cells but are now recognized as active participants in neurotransmitter release and neuronal communication [45]. Gliotransmission, the release of neurotransmitters such as GABA and glutamate by astrocytes, plays a pivotal role in maintaining brain function and homeostasis [46-48].

A breakthrough in this field was the identification of a channel-mediated mechanism that allows astrocytes to release GABA, the primary inhibitory neurotransmitter in the CNS, particularly in the cerebellum. The Best1 channel was found to facilitate this release, establishing that astrocytes contribute to tonic GABA inhibition in the cerebellum, a region crucial for motor control [49-51]. This discovery highlighted how astrocytes modulate neuronal activity, maintaining a balance between excitation and inhibition within cerebellar circuits, which is essential for motor coordination [52,53].

Further research uncovered that GABA biosynthesis in astrocytes involves the putrescine degradation pathway, with MAO-B playing a key role in converting putrescine to GABA [17]. This previously unrecognized pathway underscores the adaptability of astrocytes in regulating neurotransmitter availability and neuronal activity, reinforcing their central role in brain homeostasis.

Astrocytes' tonic GABA release is crucial for maintaining inhibitory control over neuronal activity, particularly in the cerebellum, where precise motor control is necessary for coordinated movement. Disruptions in this balance can lead

to motor deficits, such as cerebellar ataxia [53,54], highlighting the importance of astrocytic GABA in both normal and pathological motor function.

The pathological role of astrocytic GABA has been explored in various neurodegenerative diseases, including AD, PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [55,56]. In AD, aberrant GABA releases in the hippocampus impairs memory formation, while in PD, dysregulated release disrupts basal ganglia function, leading to motor deficits. Similar alterations in HD and ALS contribute to motor dysfunction and cognitive decline [57-59]. These findings suggest that astrocytic GABA is crucial for healthy brain function and may serve as a promising biomarker for diseases such as AD and PD. Targeting pathways like MAO-B and Best1 offers potential therapeutic strategies.

Beyond AD and PD, modulating astrocytic GABA may have therapeutic benefits for other neurological conditions. In white matter stroke, astrocytes may influence the maladaptive response to ischemic injury, while in spinal cord injury, GABA release may impact recovery by modulating plasticity-related circuits [60,61]. In metabolic disorders like obesity, dysregulated astrocytic neurotransmitter release can alter circuits involved in appetite and energy balance [62,63]. Additionally, in epilepsy, disruptions in GABA release can exacerbate seizures, underscoring the importance of GABAergic signaling in controlling neural excitability [64,65].

As research advances, it may open new avenues for restoring astrocytic GABA balance in neurological disorders. Targeting molecular pathways that regulate GABA release, such as MAO-B and Best1, could help restore proper GABAergic signaling, offering therapeutic potential for patients with neurodegenerative diseases, epilepsy, and other conditions. These insights highlight the promising future of therapeutic interventions aimed at modulating astrocytic function to restore neural circuit balance and alleviate symptoms in a variety of neurological disorders.

The varying impact of MAO-B expression across different neurological conditions, particularly the relationship between its upregulation and the resulting pathological consequences, is discussed in **Table 1**. In addition to cognitive decline and neurodegeneration in aging and AD, increased MAO-B expression in regions such as the striatum, substantia nigra, and cortex is directly associated with oxidative stress, excitotoxicity [66,67], and impaired neuronal function in conditions like PD, stroke, and traumatic brain injury (TBI). In diseases such as multiple sclerosis (MS) and ALS, elevated MAO-B expression in astrocytes and microglia promotes neuroinflammation and oxidative damage, resulting in axonal loss, compromised myelin integrity, and motor dysfunction (**Table 1**) [68,69]. The overexpression of MAO-B in these conditions suggests that its activity may be a key contributor to the progression of neurodegenerative diseases [9,70,71] and a promising avenue for therapeutic intervention.

Table 1. Impact of MAO-B Expression in Various Neurological Conditions.				
Condition	Brain Regions Affected	Role of Monoamine Oxidase B (MAO-B)	Impact	References
Aging	Cortex, hippocampus, striatum	Increased expression in astrocytes	Cognitive decline, oxidative stress, and early neurodegeneration	[72,73]
Alzheimer's Disease (AD)	Hippocampus, frontal cortex	Elevated in reactive astrocytes	Neuroinflammation, synaptic dysfunction, and neuronal loss	[18,74-76]
Parkinson's Disease (PD)	Substantia nigra pars compacta	Increased oxidative stress, elevated in astrocytes	Dopaminergic neuron degeneration, exacerbated neuroinflammation	[34,77-79]
Stroke	Peri-infarct regions	Upregulated in response to hypoxia and ischemia	Blood-brain barrier disruption, excitotoxicity, and neuronal injury	[80,81]
Traumatic Brain Injury (TBI)	Perilesional astrocytes	Increased MAO-B activity, prolonged neuroinflammatory response	Prolonged neuroinflammation, exacerbated neuronal damage	[82,83]
Multiple Sclerosis (MS)	Corticospinal tract, cerebellum, optic nerve	Elevated in reactive astrocytes and microglia	Neuroinflammation, axonal damage, and loss of myelin integrity	[84-86]
Amyotrophic Lateral Sclerosis (ALS)	Motor cortex, spinal cord	Elevated in astrocytes and microglia, promoting oxidative stress	Motor neuron degeneration, muscle weakness, and loss of motor function	[87,88]
Huntington's Disease (HD)	Striatum, cortex, globus pallidus	Overexpression in astrocytes, promoting neurodegenerative processes	Striatal atrophy, motor dysfunction, and cognitive decline	[89]

The following sections will discuss the multifaceted role of MAO-B in neurodegenerative diseases and CNS injury, emphasizing its contributions to oxidative stress, neuroinflammation, and neurotransmitter dysregulation. Particular attention will be given to its involvement in Parkinson's disease and Alzheimer's disease, where MAO-B activity disrupts dopaminergic and GABAergic signaling, exacerbating disease progression. Additionally, its role in CNS injury will be examined, focusing on how MAO-B-driven H₂O₂ production promotes astrocyte reactivity and glial scar formation, which, while protective, also impairs neuronal recovery.

MAO-B in cellular metabolism: Implications for glycolysis and astrocytic GABA synthesis

MAO-B is recognized for its role in the oxidative deamination of neurotransmitters and biogenic amines. Although it is not directly involved in glycolysis, emerging evidence suggests that MAO-B activity influences metabolic pathways that intersect with glycolytic processes and cellular energy homeostasis [14,90]. This connection is particularly relevant in astrocytes, where MAO-B significantly contributes to GABA synthesis.

Located on the outer mitochondrial membrane, MAO-B catalyzes the breakdown of amines, generating H₂O₂ as a byproduct. The accumulation of H₂O₂ can induce oxidative stress, impair mitochondrial function, and reduce ATP

production [91]. In response, cells may upregulate glycolysis as a compensatory mechanism to sustain energy production [92,93]. In astrocytes, such metabolic shifts can profoundly affect neurotransmitter biosynthesis, especially in the conversion of glutamate to GABA [94,95].

Beyond its direct oxidative role, MAO-B activity also impacts cellular redox signaling, which can, in turn, influence glucose metabolism. H₂O₂ has been shown to activate hypoxia-inducible factor 1-alpha (HIF-1α), a key transcription factor that regulates the expression of glycolytic enzymes [41]. The upregulation of HIF-1α promotes increased glucose uptake and enhances glycolytic flux [96,97], suggesting a potential metabolic adaptation in astrocytes under oxidative stress. This shift may alter the availability of metabolic intermediates required for GABA synthesis, potentially disrupting the balance of inhibitory neurotransmission.

In neurodegenerative diseases such as Alzheimer's and Parkinson's, elevated MAO-B activity, oxidative stress, and significant metabolic alterations in astrocytes are commonly observed [9,34,71,98]. The increased expression of glycolytic enzymes in these conditions points to a reprogramming of astrocytic metabolism [43,99], potentially as a direct consequence of MAO-B activity or as an adaptive response to mitochondrial dysfunction. This metabolic reprogramming may disturb the delicate balance of neurotransmitter synthesis, including astrocytic GABA production, further exacerbating disease pathology.

Regulation of oxidative stress by MAO-B and H₂O₂: Implications for neurodegenerative diseases

H₂O₂, produced by MAO-B, plays a critical role in regulating oxidative stress by triggering a cascade of cellular defense mechanisms [100]. This includes the upregulation of key antioxidant enzymes such as catalase, superoxide dismutase (SOD), and peroxidase, which collectively work to neutralize oxidative damage and maintain redox balance [101]. Astrocytes, known for their robust antioxidant capacity, serve as first-line responders to oxidative stress by enhancing the expression and activity of these enzymes [94]. This protective mechanism is essential for shielding neurons from oxidative damage and preserving synaptic integrity [102].

However, under pathological conditions such as Alzheimer's and Parkinson's disease, chronic MAO-B activation leads to excessive and sustained H₂O₂ production, along with other ROS [6,103]. Over time, this persistent oxidative burden overwhelms the cellular antioxidant defense system, resulting in mitochondrial dysfunction, lipid peroxidation, protein aggregation, and DNA damaged hallmark features of neurodegenerative disease pathology [104]. As oxidative stress intensifies, neuronal function becomes increasingly compromised, accelerating disease progression and cognitive decline [105].

Targeting MAO-B represents a promising therapeutic strategy for mitigating oxidative stress and restoring neuronal homeostasis. Pharmacological inhibitors such as selegiline and rasagiline effectively reduce H₂O₂ production [106], thereby alleviating oxidative stress and preventing cellular damage. Additionally, MAO-B inhibition has been shown to enhance endogenous antioxidant enzyme activity, reinforcing the brain's natural defense against oxidative injury [1,107]. By reducing neurotoxicity and preserving neuronal integrity, these inhibitors offer a multifaceted approach to combating neurodegenerative diseases, potentially slowing disease progression and improving clinical outcomes.

MAO-B Inhibitors in PD: Mechanisms, Dopamine Metabolism, and Astrocytic Neuroinflammation

PD is a prevalent neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, leading to reduced dopamine levels in the striatum [108,109]. This depletion manifests as hallmark motor symptoms, including bradykinesia, resting tremors, rigidity, gait disturbances, and postural instability [110-112]. While levodopa remains the primary treatment, MAO-B inhibitors, such as selegiline and rasagiline, are employed as monotherapy or adjunctive therapy [113,114]. However, their clinical efficacy remains inconsistent, highlighting the need for a deeper understanding of their role in PD pathophysiology.

Although MAO-B's precise function in dopamine degradation

is still under investigation, the therapeutic benefits of its inhibitors suggest a broader role in dopamine regulation. Emerging evidence indicates that these inhibitors primarily exert their effects by reducing tonic inhibition of dopaminergic neurons in the substantia nigra pars compacta rather than directly blocking dopamine metabolism [9,115,116]. Beyond dopamine regulation, MAO-B inhibitors may also confer neuroprotection by stabilizing mitochondria, inducing anti-apoptotic proteins, and promoting neurotrophic factors, potentially mitigating further dopaminergic neuron degeneration [114,117,118]. These findings underscore the need to reassess the mechanisms underlying MAO-B inhibition in PD to refine therapeutic strategies.

Comparative roles of MAO-A and MAO-B in dopamine metabolism and PD

Each isoform of MAOs, MAO-A and MAO-B, exhibits distinct substrate specificity, cellular distribution, and physiological roles. MAO-A is primarily localized in dopaminergic axon terminals, where it plays a key role in degrading epinephrine, norepinephrine, serotonin, and melatonin (**Table 2**) [2,9,25,119]. In contrast, MAO-B is predominantly expressed in astrocytes and serotonergic neurons, preferentially metabolizing phenylethylamine and benzylamine [8,120,121]. Although both isoforms contribute to dopamine (DA) metabolism, emerging evidence suggests that MAO-A is the principal enzyme responsible for DA degradation [2,122]. These findings challenge previous assumptions about MAO-B's role in PD and underscores the necessity of re-evaluating MAO-targeted therapeutic strategies.

Early pharmacological studies suggested MAO-B as a key regulator of DA metabolism, but genetic and biochemical analyses have refined this perspective. Studies on MAO-B-deficient mice show no significant alterations in striatal DA levels, whereas selective MAO-A inhibition markedly reduces DA metabolism [123,124]. Additionally, MAO-B inhibitors such as selegiline and rasagiline exert minimal effects on DA efflux in dopaminergic brain regions, reinforcing the role of MAO-A as the primary enzyme in DA catabolism [9,114,116,117].

Beyond DA metabolism, MAO-B is critical for astrocytic function and neuroinflammation. It facilitates the synthesis of astrocytic GABA through putrescine degradation, contributing to excessive tonic inhibition of dopaminergic neurons in the substantia nigra pars compacta, a mechanism associated with motor dysfunction in PD [125-127]. Increased MAO-B expression correlates with reactive astrogliosis, further implicating it in disease progression. The therapeutic benefits of MAO-B inhibitors may therefore stem from reducing astrocytic GABA synthesis and neuroinflammation rather than directly preserving DA levels (**Table 2**) [9,128,129].

MAO-B is also involved in neurotoxin-induced parkinsonism, specifically in the metabolism of MPTP, which selectively

Table 2. Comparative Functional and Pathophysiological Roles of MAO-A and MAO-B in Dopamine Metabolism and Neurodegenerative Diseases.			
Feature	MAO-A	MAO-B	References
Primary Location	Dopaminergic axon terminals	Astrocytes, serotonergic neurons	[30,130]
Key Substrates	Dopamine, serotonin, norepinephrine, melatonin	Phenylethylamine, benzylamine	[2,131]
Role in DA Metabolism	Major contributor to DA degradation	Limited involvement in DA degradation	[2,9]
Impact of Inhibition	Reduces DA metabolism and turnover	No significant effect on DA efflux	[132,133]
Relevance to PD	Directly affects DA availability	Implicated in astrocytic GABA synthesis and neuroinflammation	[2,9,126]
Expression Regulation	Modulated by hormonal and environmental factors	Upregulated in aging and neurodegeneration	[120,134,135]
Role in Oxidative Stress	Generates hydrogen peroxide (H ₂ O ₂)	Contributes to oxidative stress in astrocytes	[34,136]
Association with Neurodegenerative Diseases	Implicated in depression, anxiety, PD	Involved in PD, Alzheimer's, and neuroinflammation	[121,130]
Role in MPTP Neurotoxicity	Minimal involvement	Convert MPTP into toxic MPP ⁺ , damaging DA neurons	[9,137]
Neurotransmitter Turnover Rate	Rapid metabolism of monoamines	Slower turnover, mainly in glial cells	[124,138]
Therapeutic Implications	Targeted inhibition increases synaptic DA	Inhibition reduces astrocytic GABA overproduction	[139,140]
Pharmacological Inhibitors	Clorgyline, moclobemide	Selegiline, rasagiline	[141]

targets dopaminergic neurons [142,143]. Within astrocytes, MAO-B converts MPTP into its toxic metabolite MPP⁺, which enters dopaminergic neurons via the dopamine transporter, leading to mitochondrial dysfunction and cell death [143-145]. MAO-B inhibitors such as selegiline mitigate MPTP-induced neurotoxicity, suggesting neuroprotective mechanisms beyond DA metabolism, potentially involving mitochondrial and glial function [114,118].

These findings highlight the complex role of MAO-B in PD, extending beyond DA metabolism to astrocytic regulation and neuroinflammatory pathways.

MAO-B in PD: Astrocytic GABA regulation and oxidative stress

MAO-B has long been recognized for its role in dopamine metabolism and the activation of the neurotoxin MPTP into its toxic form, MPP⁺, contributing to PD pathogenesis. However, recent studies have expanded its functional scope beyond DA degradation, highlighting its involvement in astrocytic GABA synthesis and H₂O₂ production—both of which significantly contribute to neurodegeneration [128,146-148].

Under physiological conditions, MAO-B regulates astrocytic GABA synthesis, particularly in the cerebellum and striatum [17,149]. It catalyzes the conversion of putrescine into GABA, which is subsequently released tonically through the Ca²⁺-

activated anion channel Bestrophin-1 (Best1) [9,17]. This extrasynaptic GABA exerts inhibitory effects on neighboring neurons, with a region-specific distribution favoring the striatum and cerebellum [150,151]. Unlike MAO-B, MAO-A does not participate in astrocytic GABA-mediated inhibition in the striatum, reinforcing MAO-B's specialized role in modulating neuronal excitability [2,152].

In PD, reactive astrogliosis leads to increased MAO-B expression in the substantia nigra pars compacta (SNpc), driving excessive astrocytic GABA synthesis and abnormal tonic inhibition of dopaminergic neurons [9,126,153]. This pathological inhibition suppresses neuronal activity and downregulates tyrosine hydroxylase (TH), a key enzyme in DA synthesis [129,154]. While TH suppression is reversible in viable neurons, prolonged inhibition exacerbates DA depletion and contributes to PD-associated motor deficits [10,77,155].

Beyond GABA synthesis, MAO-B also catalyzes the degradation of N-acetylputrescine, generating H₂O₂ as a metabolic byproduct [1,9]. Excessive H₂O₂ in PD exacerbates neurodegeneration by promoting oxidative stress, enhancing astrocytic reactivity, and accelerating dopaminergic neuron loss [34,90,156]. Experimental evidence from MPTP mouse models suggests that scavenging H₂O₂ can mitigate neurodegeneration, further implicating MAO-B-mediated oxidative stress in PD pathology [79,143,156].

The emerging understanding of MAO-B’s role in astrocytic GABA regulation and oxidative stress has redefined its contribution to PD, shifting the focus beyond DA metabolism. These findings establish MAO-B as a key player in pathological astrocytic signaling and highlight its potential as a therapeutic target in PD.

The Role of MAO-B in GABA Regulation and AD Pathogenesis

MAO-B has emerged as a crucial factor in the dysregulation of GABAergic signaling in AD [70,71]. As an enzyme responsible for the oxidative deamination of neurotransmitters, such as dopamine and serotonin, MAO-B produces ROS as byproducts, contributing significantly to oxidative stress in the brain. Under normal conditions, MAO-B is present at low levels in the brain, but its expression is markedly upregulated in reactive astrocytes during neurodegenerative diseases, including AD [71,98,140,157]. The increased activity of MAO-B in these

glial cells has profound implications for neurotransmitter metabolism and neuronal health, particularly in the context of GABA regulation (Table 3) [2,118,158].

In AD, the overexpression of MAO-B in reactive astrocytes exacerbates oxidative stress, which disrupts GABAergic signaling [71,74,164]. GABA is essential for regulating neuronal excitability and maintaining synaptic balance [165,166]. Astrocytes are responsible for maintaining GABA homeostasis through the uptake and clearance of excess GABA from the synaptic cleft via GABA transporters (GATs) [39,148]. However, elevated MAO-B activity generates ROS that can damage these transporters, impairing their ability to effectively clear GABA from the synaptic space [167,168]. This impairment leads to the accumulation of extracellular GABA, which disrupts the balance between excitatory and inhibitory signaling in the brain, resulting in neuronal hyperexcitability and contributing to the cognitive deficits observed in AD (Table 3) [169-171].

Table 3. Impact of MAO-B Activity on Astrocytic GABA Regulation in Alzheimer's Disease Pathogenesis.					
Key Element	Description	Mechanisms Involved	Implications for AD Pathophysiology	Therapeutic Considerations	References
MAO-B Activity in Astrocytes	MAO-B is overexpressed in reactive astrocytes in AD, leading to oxidative stress and disrupted GABA metabolism.	MAO-B deaminates neurotransmitters like dopamine, generating reactive oxygen species (ROS) as byproducts.	Elevated MAO-B activity exacerbates oxidative stress, impairing GABA metabolism and synaptic function.	Inhibiting MAO-B could reduce oxidative stress and restore GABAergic balance in AD.	[12,44,70]
MAO-B and GABA Transporters	MAO-B activity impairs GABA transporters (GATs) in astrocytes, reducing the reuptake of GABA from the synaptic cleft.	MAO-B-induced ROS damage compromises GAT-1 function, leading to abnormal accumulation of GABA.	Dysregulated GABA uptake contributes to excessive extracellular GABA, worsening excitatory-inhibitory imbalance.	Restoring GAT function or reducing MAO-B activity may help re-establish proper GABAergic tone.	[12,159]
MAO-B and GABA Synthesis	Increased MAO-B activity in astrocytes reduces the synthesis of GABA by disrupting the enzymatic processes.	MAO-B-induced oxidative stress damages enzymes involved in GABA synthesis, such as GAD.	Impaired GABA synthesis contributes to reduced inhibitory signaling, promoting neuronal hyperactivity.	Targeting MAO-B to alleviate oxidative damage could enhance GABA synthesis and improve inhibition.	[2,17,160]
MAO-B and GABA Receptor Function	MAO-B overexpression in astrocytes affects GABA receptor expression and function, impairing synaptic plasticity.	Altered GABA-A and GABA-B receptor function due to ROS accumulation from MAO-B activity.	Dysfunctional GABA receptors exacerbate synaptic dysfunction, impairing plasticity and cognitive processes.	Pharmacologically targeting GABA-A and GABA-B receptors could mitigate synaptic dysfunction in AD.	[12,74]
MAO-B and Astrocyte-Neuron Interactions	MAO-B influences astrocytic support for neurons, affecting synaptic GABAergic function in AD.	Reactive astrocytes with high MAO-B activity affect neuronal excitability and GABAergic signaling.	MAO-B-induced damage to astrocytes disrupts their ability to modulate neuronal activity, exacerbating neurodegeneration.	Modulating MAO-B could protect astrocyte-neuron interactions and maintain GABAergic signaling.	[12,17,161]

MAO-B and Neuroinflammation	Elevated MAO-B activity enhances pro-inflammatory cytokine release from astrocytes, exacerbating AD pathology.	MAO-B activity in astrocytes stimulates inflammatory pathways, contributing to neuroinflammation.	Neuroinflammation worsens GABAergic dysfunction, leading to synaptic loss and cognitive decline.	Inhibiting MAO-B could reduce neuroinflammation, improving GABAergic function and slowing AD.	[18,70,162]
MAO-B and Excitotoxicity	MAO-B-induced oxidative stress promotes neuronal hyperexcitability by impairing GABAergic inhibition.	The ROS produced by MAO-B activity in astrocytes leads to neuronal overactivation and excitotoxicity.	Impaired GABAergic inhibition due to MAO-B activity increases the risk of excitotoxicity and neuronal damage.	MAO-B inhibition could protect neurons from excitotoxic damage by restoring GABAergic function.	[71,118]
Therapeutic Potential: MAO-B Inhibition	MAO-B inhibitors, such as selegiline, have shown potential in reducing oxidative stress and restoring GABAergic balance.	MAO-B inhibitors decrease ROS production, protecting GABA transporters and improving synaptic function.	Inhibiting MAO-B may improve cognitive function, reduce neuroinflammation, and alleviate oxidative damage.	Selegiline and similar MAO-B inhibitors could provide therapeutic benefit in AD by restoring GABA signaling.	[71,114,163]
Alternative Therapeutic Strategies	Targeting GABA-A or GABA-B receptors on astrocytes may restore GABAergic signaling disrupted by MAO-B.	Modulating GABA receptor function on astrocytes can help re-establish inhibitory control.	Restoring proper GABAergic tone could protect against cognitive decline and neurodegeneration in AD.	Developing drugs to modulate astrocytic GABA receptors could complement MAO-B inhibition for AD therapy.	[39,160]

The role of MAO-B in GABA metabolism is not limited to its effect on GABA transporters. The enzyme's activity also affects GABA synthesis. ROS generated by MAO-B can inhibit key enzymes involved in GABA production, thereby reducing the availability of GABA in the brain [71,161,169]. This reduction further exacerbates GABAergic dysfunction and enhances neuronal excitability, ultimately accelerating neurodegenerative processes in AD [17]. Additionally, MAO-B-mediated oxidative stress can interfere with the functionality of GABA receptors, such as GABA-A and GABA-B receptors, which are involved in astrocyte responses to GABAergic activity (**Table 3**) [12,39,172]. Disruption of GABA receptor signaling impairs communication between astrocytes and neurons, compounding the GABAergic dysregulation seen in AD and contributing to the neurodegenerative cascade [74,171,173,174].

Furthermore, MAO-B-induced oxidative stress may have a synergistic effect when coupled with other pathophysiological processes in AD, such as the accumulation of amyloid- β ($A\beta$) plaques [175,176]. $A\beta$ plaques are known to trigger inflammatory responses in astrocytes, leading to reactive gliosis and further upregulation of MAO-B [70,74,150]. This creates a vicious cycle in which MAO-B activity promotes oxidative damage, which in turn exacerbates the neuroinflammation and GABAergic dysfunction characteristic of AD (**Table 3**) [12,74]. As oxidative stress accumulates contributing to the progression of cognitive decline and neurodegeneration.

Given the central role of MAO-B in GABAergic dysfunction and oxidative stress, it has become an attractive therapeutic target for AD. Inhibiting MAO-B activity could potentially reduce ROS production, restore GABA homeostasis, and alleviate the neuronal excitability that drives neurodegeneration. Several MAO-B inhibitors are already used in the treatment of PD, and their application in AD holds promise for modulating oxidative stress and improving GABAergic signaling (**Table 3**). Furthermore, understanding the molecular mechanisms that govern MAO-B expression and activity in astrocytes could provide new insights into the pathogenesis of AD and lead to the development of more targeted and effective treatments.

Role of MAO-B in Astrocyte Reactivity and Glial Scar Formation Following CNS Injury

MAO-B plays a critical role in astrocyte reactivity and glial scar formation, key processes in the brain's response to injury [82,177]. Reactive astrocytes undergo substantial morphological and biochemical changes, such as hypertrophy and metabolic reprogramming, which are necessary for the formation of glial scars that help isolate the injured area [178,179]. One of the central mediators in this process is H_2O_2 , a by-product of various enzymatic reactions, which is thought to be instrumental in initiating astrocytic hypertrophy and scar formation [152,180]. MAO-B contributes to H_2O_2 production, which is associated with astrocyte dysfunction and the progression of glial scar formation [153,177].

Astrocyte reactivity is tightly controlled by specific enzymatic pathways, with the MAO-B-H₂O₂ signaling axis playing a pivotal role in driving astrocytic hypertrophy and proliferation [90,148,181]. Increased MAO-B activity leads to higher H₂O₂ production, which in turn promotes the transformation of astrocytes into a hypertrophic, scar-forming phenotype [34,153]. This process is further influenced by interactions between reactive astrocytes and other cell types, such as microglia, which collectively contribute to the inflammatory response following CNS injury. Inhibiting MAO-B activity has shown potential in reducing astrocyte reactivity and glial scar formation, highlighting the therapeutic potential of targeting this pathway in neurodegenerative diseases and CNS injuries [82,150,153].

While glial scars formed by reactive astrocytes serve a protective role by isolating damaged regions and preventing further neuronal injury, they also hinder axonal regeneration, complicating recovery. Reactive astrocytes exhibit varying degrees of reactivity, from mild hypertrophy to more severe hypertrophy and proliferation, likely due to the activation of different metabolic pathways. Balancing the reduction of scar formation while maintaining the protective functions of astrocytes is a significant challenge. Modulating MAO-B activity offers a potential strategy to shift astrocytes toward a less reactive state, thereby mitigating the adverse effects of glial scar formation while preserving their critical neuroprotective roles in the injury response.

Monoamine Oxidase B in Astrocytic GABA Synthesis and Cancer Biology

MAO-B is recognized for its role in neurotransmitter metabolism within the central nervous system. However, recent studies have expanded its significance, revealing it as a crucial player in various cancer-related processes [182]. In addition to its established neurobiological functions, MAO-B has been implicated in cancer progression, particularly through its regulation of oxidative stress, modulation of the tumor microenvironment (TME), and influence on cellular dynamics [183]. Notably, MAO-B's involvement in astrocytic GABA synthesis adds further complexity to neuro-oncological contexts, such as gliomas, where it may mediate interactions between neurons and glial cells, ultimately affecting tumor behavior.

Mechanisms of MAO-B in cancer biology

One of the primary mechanisms through which MAO-B contributes to cancer progression is its regulation of ROS. MAO-B catalyzes the breakdown of biogenic amines, including dopamine, generating hydrogen peroxide as a byproduct [107]. This process leads to the accumulation of ROS, which induces oxidative stress, an established factor in cancer development [184]. The accumulation of ROS can result in DNA damage, activation of inflammatory responses,

and disruption of cellular signaling, all of which promote genomic instability and create a microenvironment conducive to malignant transformation [184]. By enhancing oxidative stress, MAO-B thus facilitates early-stage cancer development and tumor progression.

In addition to ROS regulation, MAO-B overexpression is commonly observed in various cancers, where it influences the TME [41]. MAO-B alters metabolic reprogramming [2,185] by shifting the balance between aerobic and anaerobic metabolism—processes that are essential for cancer cell survival and proliferation. This metabolic shift contributes to therapeutic resistance. Moreover, the inflammatory environment generated by MAO-B activity further complicates the TME [103,186], promoting immune evasion and enhancing metastatic potential. Thus, MAO-B becomes integral to the maintenance of the malignant state, supporting both local tumor growth and metastatic spread.

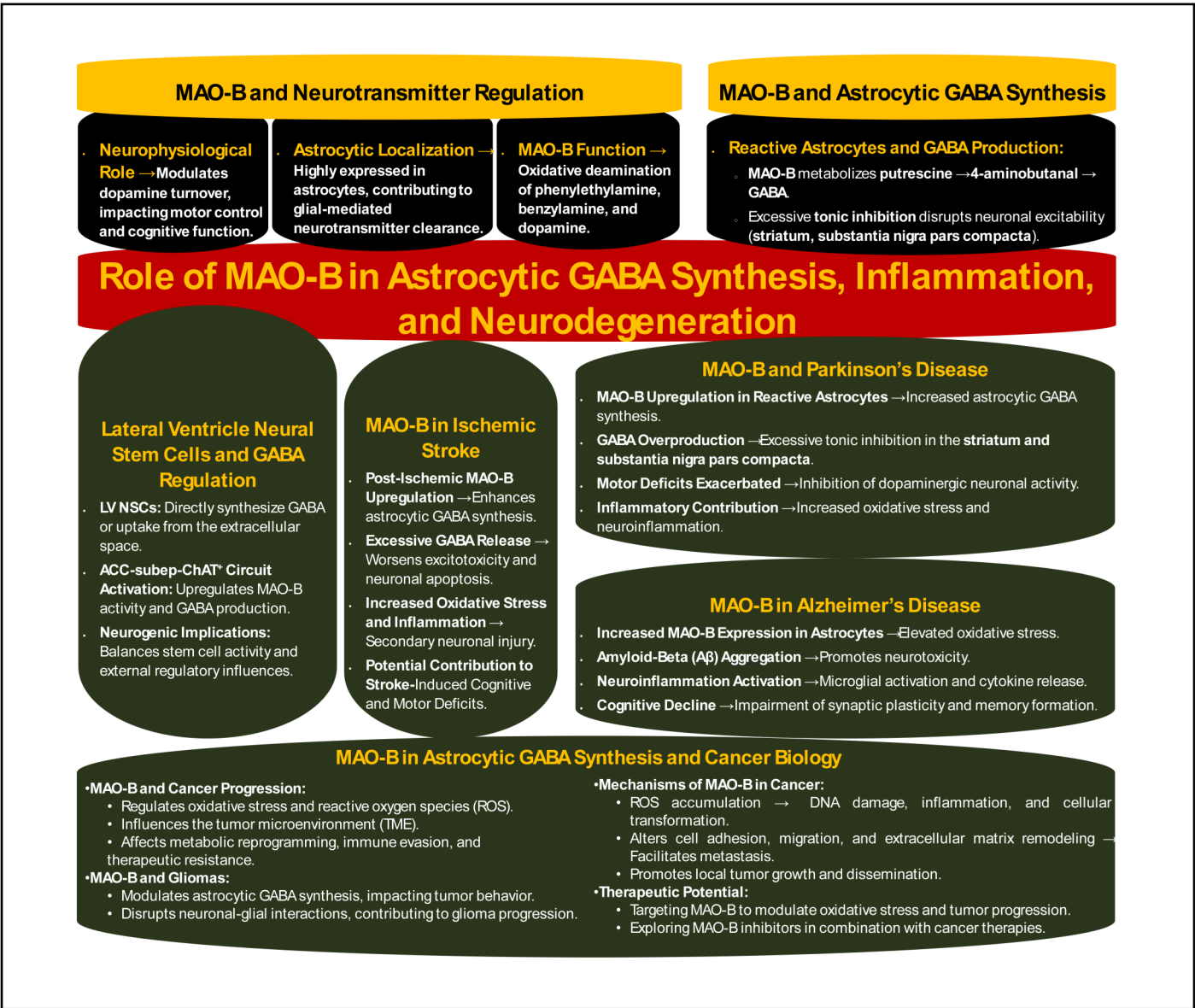
MAO-B also affects cancer cell motility and invasion [187], which are crucial factors in metastasis. By modulating key signaling pathways related to cell adhesion, migration, and extracellular matrix remodeling, MAO-B enhances the ability of cancer cells to invade surrounding tissues and spread to distant organs. This metastatic potential underscores MAO-B's critical role not only in local tumor growth but also in cancer cell dissemination [182].

MAO-B in astrocytic GABA synthesis and cancer

Beyond its role in cancer biology, MAO-B plays a critical role in neurotransmitter metabolism, particularly in the synthesis of GABA [9]. Within astrocytes, MAO-B is involved in the catabolism of GABA precursors, such as the conversion of glutamate to glutamine [38,188], which is subsequently utilized in GABA synthesis. This process is essential for maintaining the balance of neurotransmitter pools in the brain, particularly in regions responsible for regulating neuronal excitability and synaptic plasticity, such as the cortex and hippocampus.

The involvement of MAO-B in astrocytic GABA synthesis takes on particular significance in brain tumors, especially gliomas, where the balance between excitatory and inhibitory signals is often disrupted [39]. In these tumors, altered astrocytic function, including changes in GABAergic signaling [189,190], may be influenced by MAO-B activity. Dysregulation of GABAergic signaling in gliomas can significantly affect tumor cell behavior, including proliferation, survival, and communication between tumor cells and surrounding glial cells [191]. This disruption may contribute to abnormal TME, which supports tumor growth and resistance to therapies.

Furthermore, astrocytic GABA synthesis is essential for proper neuronal-glial communication [39]. In gliomas, this communication is often impaired, and the altered GABAergic signaling can affect the functional interactions between glial cells and tumor cells. Such dysregulation complicates



the tumor's response to treatment, further emphasizing the complex role of MAO-B in regulating astrocytic GABA synthesis within brain tumors.

Discussion and Concluding Remarks

MAO-B plays a multifaceted role in neurological health and disease, impacting both neurotransmitter regulation and neuroinflammatory processes. As highlighted in this article, MAO-B is essential for the oxidative deamination of key monoamines such as dopamine, noradrenaline, and serotonin, but it also significantly influences astrocytic modulation of neurotransmitter signaling, particularly GABA. The article explores the dual nature of MAO-B activity: while it is vital for maintaining normal brain function, its dysregulation can lead to neuroinflammation, oxidative stress, and neuronal damage, contributing to the pathophysiology of a range of neurological disorders, including AD, PD, HD, and ALS.

In neurodegenerative diseases such as AD and PD, heightened MAO-B activity in astrocytes leads to the generation of ROS, including hydrogen peroxide, which exacerbates oxidative stress and GABAergic dysfunction. This disruption of neurotransmitter balance accelerates neuronal loss and impairs neuronal recovery. The article also discusses how MAO-B-induced glial reactivity contributes to the formation of glial scars, which, while protective, hinder axonal regeneration and recovery. Targeting these scars offers a promising therapeutic intervention.

Future research should focus on uncovering the mechanisms through which MAO-B modulates neuroinflammation and neurotransmitter imbalances, particularly within reactive astrocytes. Examining how MAO-B activity affects neuronal function in specific brain regions, such as the hypothalamus and cerebellum, could provide critical insights into disease-specific pathophysiology and potential therapeutic targets.

Additionally, the therapeutic potential of MAO-B inhibitors, which have shown promise in alleviating symptoms and slowing disease progression in conditions like PD, should be further explored in clinical trials to determine their efficacy in a broader range of neurodegenerative and neuroinflammatory diseases.

Identify MAO-B as a potential enzyme responsible for synthesizing GABA within LV NSCs, which regulate their homeostatic proliferation through neural circuit activity. This discovery could provide deeper insights into glioblastoma and its regulation by neural circuits, given its presumed origin in LV NSCs. Furthermore, investigating whether glioblastoma synthesizes GABA, whether this synthesis occurs through MAO-B, and how GABA contributes to glioblastoma's sustained growth and progression warrants further exploration.

The enzymatic activity of MAO-B in tumors influences aberrant signaling pathways, contributing to tumor growth, treatment resistance, and metastasis. These findings suggest that MAO-B inhibitors may serve as potential therapeutic agents in cancer treatment. Early studies have shown that inhibiting MAO-B suppresses cancer cell proliferation across various tumor types, highlighting a promising approach to targeting oxidative stress and tumor dynamics driven by MAO-B. The dual role of MAO-B in both cancer biology and neurotransmitter metabolism offers new insights into the intricate relationship between the nervous system and cancer. Additionally, understanding the impact of MAO-B on astrocytic GABA synthesis in brain tumors provides valuable perspectives on the molecular mechanisms governing tumor behavior and neuron-glial interactions. Modulating MAO-B's enzymatic activity may help address both oxidative stress and neurotransmitter imbalances in tumors, paving the way for innovative therapeutic strategies in neuro-oncology.

One limitation of the current body of research is the complexity of MAO-B's dual role in both neurotransmitter regulation and neuroinflammation. The effects of MAO-B upregulation in reactive astrocytes are context-dependent and may vary across different neurological conditions, complicating our understanding of its precise role at various stages of disease progression. Furthermore, although MAO-B inhibitors have demonstrated therapeutic potential, their inconsistent efficacy underscores the need for a more nuanced approach to targeting MAO-B without disrupting essential brain functions.

To address these gaps, future studies should aim to clarify the temporal dynamics of MAO-B activity in neurodegenerative diseases, assessing whether modulation in the early stages offers protective effects or if sustained inhibition could prevent progression in later stages. Longitudinal studies, coupled with advanced imaging technologies, may provide valuable insights into the impact of MAO-B inhibition on neuroinflammation, synaptic plasticity, and astrocyte function.

Moreover, expanding research into the effects of MAO-B modulation in other conditions, such as metabolic disorders and traumatic brain injury, could broaden the therapeutic potential of targeting this enzyme.

MAO-B is a pivotal enzyme with profound implications for both brain health and the pathogenesis of neurological diseases. While its upregulation in reactive astrocytes contributes to neurodegeneration by exacerbating oxidative stress and disrupting GABAergic signaling, MAO-B also represents a promising therapeutic target for neurodegenerative disorders. This article highlights the potential of MAO-B inhibitors to slow disease progression and restore neurotransmitter homeostasis. However, it emphasizes the necessity of a more refined understanding of MAO-B's complex and context-dependent roles in brain function. Future research should prioritize elucidating the mechanisms that govern MAO-B regulation across various neurological conditions, with the aim of optimizing its therapeutic targeting in neurodegenerative and metabolic diseases.

Declarations

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M.M.N. contributed to the design and writing of the main manuscript text.

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