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Review

Targeting Metabolic Pathways for Neurodegeneration: The Emerging Role of Anti-Diabetic and Lipid-Lowering Agents

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Abstract

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) represent a significant and growing global health burden. Despite extensive research, effective disease-modifying therapies remain elusive. Recent insights into the shared pathophysiological pathways between metabolic syndromes and neurodegeneration particularly mitochondrial dysfunction, insulin resistance, oxidative stress, and chronic inflammation have opened new therapeutic opportunities. The concept of drug repurposing, wherein existing anti-metabolic drugs like anti-diabetics and lipid-lowering agents are evaluated for neuroprotective efficacy, offers a promising translational route to accelerate therapeutic discovery. Agents such as metformin, pioglitazone, GLP-1 receptor agonists, and statins have demonstrated neurorestorative and anti-inflammatory effects in preclinical and early clinical settings. Moreover, AMP-activated protein kinase (AMPK) activation, peroxisome proliferator-activated receptor gamma (PPARγ) modulation, and enhancement of insulin signaling appear central to their neuroprotective mechanisms. This review consolidates mechanistic evidence, preclinical data, and emerging clinical trials supporting the repositioning of anti-metabolic agents for neurodegenerative disease modification, with a focus on molecular pathways, pharmacodynamic interactions, and translational challenges. It also highlights future perspectives, emphasizing combinatorial and precision medicine strategies integrating metabolomics, neuroimaging, and artificial intelligence to optimize therapeutic repurposing for neurodegenerative diseases.

Keywords: Drug repurposing, neurodegenerative diseases, anti-diabetic drugs, lipid-lowering agents, insulin resistance, mitochondrial dysfunction

1.0 Introduction

Neurodegenerative diseases represent a constellation of progressive disorders characterized by the selective loss of neuronal populations, accumulation of misfolded proteins, and failure of neuroprotective homeostatic mechanisms. Despite the heterogeneity in their clinical presentations, including memory impairment in Alzheimer's disease, dopaminergic neuronal loss in Parkinson's disease, or motor neuron degeneration in amyotrophic lateral sclerosis, convergent molecular mechanisms such as mitochondrial dysfunction, aberrant protein folding, endoplasmic reticulum stress, and neuroinflammation are consistently observed across the neurodegenerative spectrum [1]. Epidemiological and experimental data suggest a compelling link between metabolic syndromes, including type 2 diabetes mellitus (T2DM), dyslipidemia, and obesity, with accelerated neurodegeneration [2]. Insulin resistance, once considered confined to peripheral tissues, is now recognized as a crucial factor in the brain, impairing neuronal glucose uptake and leading to cognitive decline and synaptic dysfunction a phenomenon often termed "type 3 diabetes" in Alzheimer's pathogenesis [3]. The brain's high metabolic demand and reliance on oxidative phosphorylation render it particularly vulnerable to metabolic derangements, implicating systemic metabolic stress as a driver of neuronal injury.

Within this framework, repurposing anti-metabolic agents has emerged as an attractive therapeutic paradigm. By targeting shared molecular pathways such as AMPK activation, peroxisome proliferator-activated receptor (PPAR) regulation, and lipid homeostasis, anti-diabetic and lipid-lowering drugs offer neuroprotective effects beyond their primary indications. The advantage of drug repurposing lies in leveraging existing safety profiles, known pharmacokinetics, and clinical experience, thereby reducing the time and cost associated with novel drug discovery [4]. In particular, biguanides, thiazolidinediones, incretin-based therapies, and statins have demonstrated mechanistic and clinical promise for slowing neurodegenerative progression.

1.1 The Concept of Drug Repurposing in Neurology

Drug repurposing, also referred to as drug repositioning, involves identifying new therapeutic indications for existing pharmacological agents. This strategy is particularly relevant in neurology, where conventional drug development faces high attrition rates, often exceeding 90%, due to the complexity of central nervous system (CNS) pathophysiology and the impermeability of the blood–brain barrier (BBB) [5]. Repurposing allows researchers to capitalize on previously established pharmacological and toxicological data, expediting clinical translation.From a neurotherapeutic perspective, the metabolic–neurological interface presents an ideal platform for repurposing investigations. Drugs originally designed to modulate systemic glucose and lipid metabolism have demonstrated pleiotropic effects on oxidative stress, mitochondrial biogenesis, and neuroinflammatory regulation [6]. Moreover, several anti-metabolic drugs cross the BBB or exert indirect neuroprotective actions via systemic metabolic modulation. The integration of computational approaches such as transcriptomic matching, in silico docking, and network pharmacology has further accelerated the identification of candidate agents with potential disease-modifying effects in the CNS [7].

The global repurposing effort has gained momentum with increasing access to pharmacovigilance data and real-world clinical outcomes. For instance, retrospective analyses have identified lower incidences of dementia in diabetic patients receiving metformin or pioglitazone compared to those treated with sulfonylureas [8]. Similarly, lipid-lowering therapies, particularly statins, have been associated with reduced risk and delayed progression of Parkinson's and Alzheimer's diseases in several population-based studies [9]. These observations underscore the translational relevance of exploring metabolic modulators as neuroprotective agents.

1.2 Metabolic Dysfunction as a Driver of Neurodegeneration

The intersection between metabolic dysregulation and neurodegeneration is grounded in the central role of energy metabolism in maintaining neuronal viability. Neurons are highly energy-demanding cells that rely on efficient glucose utilization and mitochondrial oxidative phosphorylation to sustain synaptic transmission, membrane potential maintenance, and neurotransmitter synthesis [10]. In metabolic syndromes, chronic

hyperglycemia, insulin resistance, and dyslipidemia trigger systemic oxidative stress, impair mitochondrial function, and activate pro-inflammatory signaling cascades that collectively damage neuronal integrity.

At the molecular level, insulin signaling in the brain regulates synaptic plasticity, learning, and memory through modulation of the phosphoinositide 3-kinase (PI3K)–Akt pathway and glycogen synthase kinase-3β (GSK-3β) [11]. Impairment of this pathway leads to tau hyperphosphorylation, amyloid-beta (Aβ) aggregation, and synaptic loss hallmarks of Alzheimer's pathology. Similarly, in Parkinson's disease, mitochondrial complex I dysfunction and lipid dysregulation are intimately linked to α-synuclein aggregation and dopaminergic neuronal loss [12]. Furthermore, chronic systemic inflammation associated with metabolic disorders induces neuroinflammatory responses mediated by activated microglia and astrocytes, leading to the release of cytokines such as interleukin-1β, tumor necrosis factor-alpha (TNF-α), and interleukin-6, which further exacerbate neuronal injury [13]. Dysregulated cholesterol homeostasis has also been implicated in amyloidogenic processing of amyloid precursor protein (APP) and impaired autophagic clearance, underscoring the role of lipid metabolism in neurodegeneration [14]. Therefore, targeting metabolic dysfunction represents a biologically rational approach for mitigating neurodegenerative processes.

1.3 Anti-Diabetic Agents as Neuroprotective Candidates

Among anti-metabolic drugs, anti-diabetic agents have been extensively evaluated for their neuroprotective and cognitive-enhancing properties. The most prominent classes include biguanides (e.g., metformin), thiazolidinediones (e.g., pioglitazone and rosiglitazone), and incretin-based therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide, exenatide, and semaglutide). These drugs act through diverse yet interlinked mechanisms that converge on mitochondrial biogenesis, oxidative stress reduction, and restoration of insulin signaling within the CNS. Metformin, a first-line therapy for T2DM, activates AMP-activated protein kinase (AMPK), a central energy sensor that enhances mitochondrial efficiency, stimulates autophagy, and suppresses inflammatory signaling through inhibition of NF-κB [15]. Preclinical studies in AD models have demonstrated that metformin attenuates tau phosphorylation, reduces Aβ deposition, and improves synaptic function [16]. Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, has shown neuroprotective efficacy by modulating microglial activation, enhancing lipid metabolism, and improving mitochondrial respiration [17]. Clinical trials, including the TOMMORROW study, have explored pioglitazone's potential in delaying the onset of mild cognitive impairment, although results have been mixed [18].

GLP-1 receptor agonists represent another promising class with both peripheral and central effects. These agents enhance neuronal insulin signaling, reduce oxidative stress, and promote neurogenesis. Liraglutide and exenatide have demonstrated neuroprotective effects in AD and PD models, with early clinical evidence suggesting improved cognitive outcomes and slowed motor decline [19]. Moreover, semaglutide, a long-acting GLP-1 analog, is currently under investigation for its ability to cross the BBB and exert direct neuronal effects [20]. Collectively, these findings underscore the potential of anti-diabetic agents to modify neurodegenerative disease trajectories through multifactorial mechanisms.

1.4 Lipid-Lowering Agents in Neuroprotection: Statins, Fibrates, and Emerging PCSK9 Inhibitors

The interplay between cholesterol metabolism and neurodegenerative processes has become increasingly evident over the past two decades. Cholesterol is essential for neuronal membrane integrity, myelin formation, and synaptogenesis, yet dysregulated cholesterol homeostasis has been implicated in amyloidogenic processing, oxidative stress, and neuroinflammation. Statins, or 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, have therefore attracted attention as potential neuroprotective agents beyond their cardiovascular indications [21]. By inhibiting mevalonate synthesis, statins reduce downstream isoprenoid intermediates critical for prenylation of small GTPases involved in inflammatory signaling, thereby exerting pleiotropic anti-inflammatory effects independent of lipid lowering [22]. Experimental studies have demonstrated that atorvastatin and simvastatin reduce amyloid-beta (Aβ) accumulation, attenuate tau phosphorylation, and improve cerebral blood flow in Alzheimer's models [23]. Epidemiological investigations have reported a reduced incidence of dementia among long-term statin users, though results remain heterogeneous due to differences in drug lipophilicity, dosage, and blood–brain barrier (BBB) permeability [24]. Lipophilic statins such as simvastatin and lovastatin are more

likely to cross the BBB, potentially explaining their superior neuroprotective efficacy compared to hydrophilic agents like pravastatin [25].

Fibrates, acting as peroxisome proliferator-activated receptor-alpha (PPARα) agonists, also hold neuroprotective potential through modulation of lipid oxidation, mitochondrial biogenesis, and inflammatory gene expression [26]. Fenofibrate has been shown to attenuate oxidative stress and protect dopaminergic neurons in MPTP-induced Parkinson's models [27]. Additionally, ezetimibe, a cholesterol absorption inhibitor, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are emerging candidates for exploration in neurodegeneration due to their ability to modulate lipid homeostasis and systemic inflammation [28]. Recent reports suggest PCSK9 expression in the brain may influence neuronal apoptosis and amyloid processing, although mechanistic clarity remains under investigation [29]. Thus, lipid-lowering therapies represent a rational adjunctive avenue for mitigating neurodegenerative pathogenesis through vascular, metabolic, and direct neuronal mechanisms.

Figure 1. Mechanistic Network of Anti-Metabolic Drug Repurposing in Neurodegenerative Disease Modification

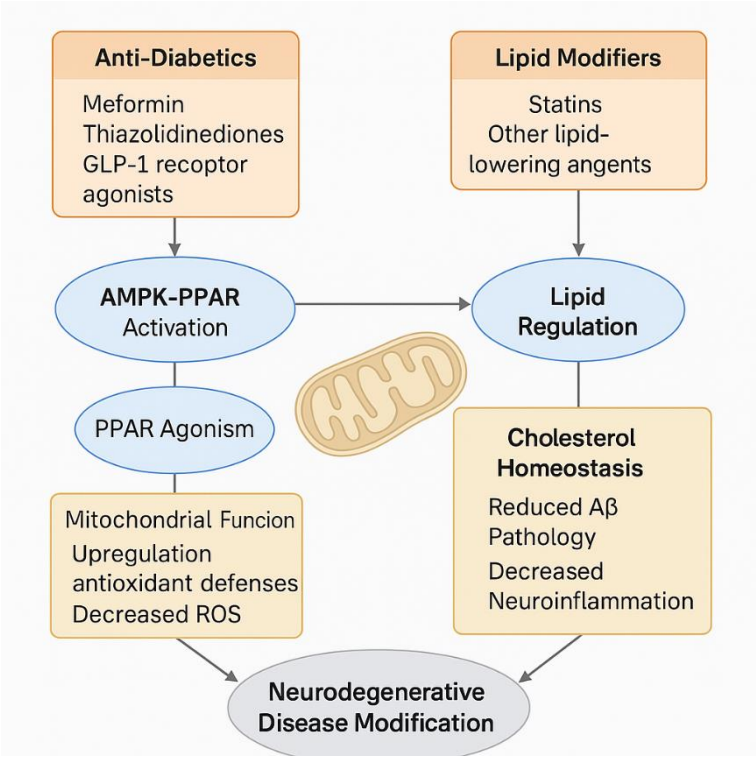

Table 1. Representative Anti-Metabolic Drugs with Neuroprotective Potential: Mechanistic Insights and Translational Status

Drug Class	Representative Agents	Primary Molecular Target(s)	Neuroprotective Mechanisms	Neurodegenerative Disease Evidence	Clinical/Translational Status
Biguanides (Anti-Diabetic)	Metformin	AMPK activation, mTOR inhibition	Enhances mitochondrial biogenesis; promotes autophagy; reduces tau phosphorylation	Alzheimer's disease (APP/PS1 mice); mild cognitive impairment trials	Mixed clinical outcomes; ongoing phase II–III studies

			and Aβ aggregation		
Thiazolidinediones (PPARγ Agonists)	Pioglitazone, Rosiglitazone	PPARγ activation	Modulates microglial activation; suppresses NF-κB; improves mitochondrial respiration	Parkinson's and Alzheimer's models; TOMMORROW and AD-4833 trials	Variable efficacy; safety concerns limit long-term use
GLP-1 Receptor Agonists (Incretin-Based)	Liraglutide, Exenatide, Semaglutide	GLP-1R activation, cAMP/CREB signaling	Restores insulin signaling; reduces oxidative stress; enhances neurogenesis	Alzheimer's (ELAD) and Parkinson's (EXENATIDE-PD3) trials show cognitive and motor improvement	Advanced clinical phase; promising translational trajectory
Statins (HMG-CoA Reductase Inhibitors)	Simvastatin, Atorvastatin, Lovastatin	Mevalonate pathway inhibition	Reduces Aβ accumulation; decreases tau phosphorylation; anti-inflammatory and vascular protective effects	Epidemiological association with reduced dementia risk; variable clinical outcomes	Widely used; under mechanistic and preventive evaluation
Fibrates (PPARα Agonists)	Fenofibrate, Gemfibrozil	PPARα activation	Enhances fatty acid oxidation; mitigates oxidative stress; modulates microglia	Preclinical evidence in Parkinson's and ALS models	Early translational evaluation; limited clinical trials
Cholesterol Absorption/PCSK9 Modulators	Ezetimibe, Evolocumab, Alirocumab	NPC1L1 and PCSK9 inhibition	Reduces systemic inflammation; stabilizes lipid homeostasis; potential modulation of amyloidogenesis	Emerging evidence in preclinical AD models	Experimental stage; mechanistic exploration ongoing
Dual PPARα/γ Agonists (Polypharmacological)	Saroglitazar, Tesaglitazar	PPARα/γ co-activation	Integrated lipid–glucose regulation; suppresses neuroinflammatory gene networks	Neuroinflammation and mitochondrial protection models	Preclinical development; potential next-generation candidates

1.5 Mechanistic Insights: AMPK, PPAR, and Mitochondrial Crosstalk in Neuroprotection

The neuroprotective effects of anti-metabolic drugs are underpinned by their convergence upon cellular energy sensors and transcriptional regulators, particularly AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPARs). AMPK serves as a metabolic master switch, responding to energy deficits by promoting ATP-generating pathways and inhibiting anabolic processes. Its activation in neuronal systems enhances mitochondrial biogenesis through upregulation of peroxisome proliferator-activated receptor gamma

coactivator-1 alpha (PGC-1α), improves autophagic clearance of misfolded proteins, and attenuates neuroinflammatory signaling [30]. Metformin-induced AMPK activation mitigates tau hyperphosphorylation by inhibiting GSK-3β, a kinase central to tau pathology in Alzheimer's disease [31]. Furthermore, AMPK interacts with sirtuin-1 (SIRT1), orchestrating a coordinated mitochondrial stress response that promotes longevity-associated transcriptional programs and neuronal survival [32]. Similarly, PPARγ agonists, including pioglitazone, exert anti-inflammatory effects by suppressing NF-κB-mediated cytokine production and promoting lipid clearance within microglia [33]. PPARα and PPARδ isoforms complement these effects by enhancing fatty acid oxidation and improving neuronal energy efficiency. Mitochondrial crosstalk represents another pivotal mechanism wherein these pathways converge. Anti-diabetic agents restore mitochondrial membrane potential, reduce reactive oxygen species (ROS) generation, and upregulate antioxidant defenses such as superoxide dismutase (SOD) and catalase [34]. In Parkinson's disease, thiazolidinediones protect dopaminergic neurons through preservation of mitochondrial complex I activity and suppression of apoptosis-inducing factor (AIF) translocation [35]. The integrated activation of AMPK, PPAR, and mitochondrial homeostatic pathways thus establishes a metabolic–neuroprotective axis capable of counteracting the energetic and oxidative imbalances that characterize neurodegenerative disorders.

1.6 Preclinical and Clinical Evidence: Translational Applications in Alzheimer's, Parkinson's, and ALS

Preclinical investigations have generated robust evidence supporting the neuroprotective effects of repurposed anti-metabolic drugs across various models of neurodegeneration. In transgenic Alzheimer's models, metformin treatment significantly reduces amyloid plaque burden and improves cognitive performance through AMPK-dependent enhancement of autophagy [36]. Liraglutide, a GLP-1 receptor agonist, has demonstrated reduction in tau phosphorylation and improved synaptic plasticity via cAMP response element-binding protein (CREB) activation [37]. In Parkinson's models, exenatide and pioglitazone confer dopaminergic neuroprotection, improve motor behavior, and mitigate microglial activation [38]. Translationally, clinical trials have yielded encouraging yet mixed results. The *EXENATIDE-PD3* study revealed sustained improvement in motor scores among Parkinson's patients after 48 weeks of exenatide treatment, even after withdrawal of therapy, suggesting disease-modifying potential [39]. Similarly, liraglutide demonstrated cognitive stabilization and improved cerebral glucose metabolism in mild Alzheimer's disease patients in the *ELAD* trial [40]. Conversely, metformin's cognitive outcomes have varied, with some studies reporting benefits in mild cognitive impairment, while others observed neutral or adverse effects potentially related to vitamin B12 deficiency or hypoglycemia [41].

For lipid-lowering drugs, the *Simvastatin in Alzheimer's Disease (CLASP)* trial did not show significant cognitive improvement, possibly due to advanced disease stage or insufficient BBB penetration [42]. However, meta-analyses suggest long-term statin use correlates with reduced dementia risk, particularly when initiated in midlife [43]. Fenofibrate's potential in amyotrophic lateral sclerosis (ALS) and Huntington's disease remains under preclinical exploration, with evidence of preserved mitochondrial function and reduced neuroinflammation [44]. Collectively, these findings indicate that therapeutic timing, disease stage, and patient metabolic profile critically influence clinical outcomes, underscoring the need for precision-based repurposing strategies.

1.7 Combination and Polypharmacological Approaches

Given the multifactorial nature of neurodegenerative pathogenesis, monotherapy is unlikely to achieve comprehensive neuroprotection. Combination strategies integrating multiple anti-metabolic agents or adjunctive neuroprotectants have shown synergistic potential. Co-administration of metformin with GLP-1 receptor agonists augments AMPK activation and enhances insulin signaling both peripherally and centrally [45]. Similarly, combining pioglitazone with statins has demonstrated additive anti-inflammatory and mitochondrial effects in experimental models of cognitive decline [46]. Polypharmacological repurposing, in which a single compound modulates multiple disease-relevant targets, aligns with contemporary drug design paradigms emphasizing network-level regulation rather than single-pathway inhibition. For instance, dual PPARα/γ agonists such as saroglitazar exhibit simultaneous lipid-lowering and anti-inflammatory activities, positioning them as promising candidates for integrated neuro-metabolic modulation [47]. Moreover, the co-targeting of metabolic and neuroinflammatory pathways can counteract both systemic and CNS-specific pathogenic drivers, providing a holistic disease-modifying framework.

Emerging therapeutic combinations may also leverage nutraceuticals and mitochondrial cofactors, such as coenzyme Q10, nicotinamide riboside, or omega-3 fatty acids, to enhance neuronal resilience and metabolic efficiency. Integration with physical exercise, caloric restriction, and intermittent fasting protocols each activating overlapping AMPK and SIRT1 pathways further illustrates the potential of multimodal metabolic interventions in neurodegenerative disease management [48]. Therefore, combinatorial strategies rooted in metabolic repurposing may hold the key to achieving durable neuroprotection.

1.8 Translational and Regulatory Challenges in CNS Repurposing

While the rationale for repurposing anti-metabolic agents in neurodegeneration is scientifically compelling, significant translational barriers persist. One of the foremost challenges is the restricted BBB permeability of many systemic agents, which limits their direct CNS bioavailability. Lipophilicity, molecular weight, and transporter affinity critically influence CNS penetration, necessitating formulation innovation such as nanoparticle encapsulation or prodrug design to enhance delivery [49]. Pharmacodynamic differences between peripheral and central tissues further complicate translational extrapolation. For example, AMPK activation in peripheral tissues enhances insulin sensitivity, whereas excessive neuronal AMPK activation under certain conditions may exacerbate neurotoxicity, indicating a delicate therapeutic window [50]. Additionally, repurposed drugs may exhibit off-target effects or pharmacokinetic interactions when combined with standard neurodegenerative therapies such as cholinesterase inhibitors or dopaminergic agents [51].

Regulatory pathways for repurposed drugs remain inconsistent across jurisdictions, often requiring new clinical trials to demonstrate efficacy in the novel indication despite established safety profiles. Intellectual property challenges also deter investment, as many repurposed drugs are off-patent, reducing commercial incentives for large-scale development [52]. Moreover, the heterogeneity of neurodegenerative diseases complicates clinical endpoint selection, demanding biomarker-driven trial designs incorporating neuroimaging, cerebrospinal fluid (CSF) metabolomics, and digital cognitive assessments [53]. Overcoming these regulatory and methodological barriers is imperative for the successful repositioning of metabolic drugs in CNS therapeutics.

1.9 Future Perspectives: Precision Metabolo-Neurotherapeutics

The future of repurposed anti-metabolic therapies for neurodegeneration lies in integrating precision medicine with systems biology. Advances in metabolomics, lipidomics, and transcriptomic profiling can identify patient subpopulations with specific metabolic signatures predictive of therapeutic responsiveness [54]. Artificial intelligence (AI) and machine learning models are being increasingly deployed to mine large-scale clinical datasets and electronic health records to identify patterns of cognitive protection associated with specific metabolic drugs [55]. Personalized polypharmacy guided by computational models may enable adaptive therapy based on real-time biomarker monitoring. For instance, dynamic adjustment of metformin or GLP-1 agonist dosing according to metabolic fluxes could optimize CNS energy homeostasis. Parallel developments in nanomedicine may enhance CNS delivery through targeted liposomal or polymeric carriers engineered for BBB traversal and sustained release [56]. From a therapeutic innovation standpoint, hybrid molecules combining metabolic and neurotrophic activity such as GLP-1/BDNF dual agonists represent the next frontier of rational drug design [57]. Future clinical trials should embrace multi-omics endpoints, digital cognitive tracking, and neuroimaging biomarkers to robustly assess disease modification. Ultimately, the repurposing of anti-metabolic drugs for neurodegenerative diseases embodies a paradigm shift toward metabolically informed neuropharmacology, bridging the gap between systemic metabolism and neuronal resilience.

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