

Review

Open Access



Age-related energetic reprogramming in glial cells: possible correlations with Parkinson's disease

Boling Chu^{1,#}, Hongling Xiang^{1,#}, Han Wang¹, Yuting Lin¹, Rui Li¹, Jing Hu^{1,2,*}, Hao Qian^{1,2,*} 

¹Sichuan Provincial Key Laboratory for Human Disease Gene Study and the Center for Medical Genetics, Department of Laboratory Medicine, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu 610054, Sichuan, China.

²School of Medicine, University of Electronic Science and Technology of China, Chengdu 610054, Sichuan, China.

#Authors contributed equally.

*Correspondence to: Prof. Hao Qian, Prof. Jing Hu, School of Medicine, University of Electronic Science and Technology of China, No.4, Section 2, North Jianshe Road, Chengdu 610054, Sichuan, China. E-mail: qianhao@uestc.edu.cn; jinghu_somed@uestc.edu.cn

How to cite this article: Chu B, Xiang H, Wang H, Lin Y, Li R, Hu J, Qian H. Age-related energetic reprogramming in glial cells: possible correlations with Parkinson's disease. *Ageing Neur Dis* 2024;4:11. <https://dx.doi.org/10.20517/and.2024.11>

Received: 11 Apr 2024 **First Decision:** 18 Jun 2024 **Revised:** 4 Jul 2024 **Accepted:** 11 Jul 2024 **Published:** 17 Jul 2024

Academic Editors: Weidong Le, David Rubinsztein **Copy Editor:** Pei-Yun Wang **Production Editor:** Pei-Yun Wang

Abstract

Glial cells populate the central nervous system and undertake indispensable roles in safeguarding and maintaining optimal neuronal performance. Throughout life, the brain undergoes inevitable changes that impact both neurons and glial cells. Concurrent with age-related neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), metabolic dysfunctions in glial cells are consistently observed. Though widely debated, the idea of treating neurodegenerative disorders by manipulating brain bioenergetics warrants further exploration. This review discusses the distinctive metabolic characteristics of central nervous system (CNS) glia, the metabolic deviations that occur in glial cells in the aging brain, and the ramifications of metabolic rewiring within glia on neurodegenerative disorders, specifically PD. We focus on astrocytes and microglia due to their substantial transformations under aging and diseased states, known as reactivation. Special attention is given to clarifying the complex relationships between dysregulated glial energy metabolism and brain disorders. By discussing both classic theories and current advances in this field, we aim to shed light on promising therapeutic horizons anchored in the strategic calibration of glial metabolic configurations.

Keywords: Glia, energy metabolism, aging, neurodegeneration, Parkinson's disease



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



INTRODUCTION

The human brain represents one of the most intricately structured tissues in complex organisms, playing a fundamental role in cognition and behavior^[1]. With advancing age, both the brain's architecture and its microenvironment undergo transformations, culminating in a gradual decline in cognitive capacities and behavioral functions, including learning, memory, and motor coordination^[2]. Neuronal degenerative diseases, characterized by neuronal loss and disruptions in network connections, are frequently associated with aging and exhibit shared underlying mechanisms^[3].

Despite comprising just 2% of overall body mass, the human brain demands an estimated 20%-25% of the body's entire energy expenditure, making it one of the most energetically costly organs within the human body^[4]. In general, glucose serves as the principal energy substrate supporting brain function. Once across the blood-brain barrier, glucose undergoes transformation into adenosine triphosphate (ATP), a vital energy currency, via dual pathways - namely glycolysis and oxidative phosphorylation (OXPHOS)^[2]. Notably, diverse cell types within the central nervous system exhibit markedly dissimilar energy metabolism profiles. Specifically, neurons primarily rely upon OXPHOS for generating ATP^[5], whereas astrocytes predominantly employ glycolysis^[6]. Moreover, neural cells possess the capacity to harness various substrates such as glutamate, glutamine, pyruvate, and lactate, thereby facilitating intricate intercellular exchange mechanisms among glial and neuronal populations^[7,8]. Such complex interactions play pivotal roles in preserving physiological equilibrium and contributing to disease etiology. Another crucial aspect meriting careful attention pertains to the dialogue between neuronal dynamics and regulatory mechanisms governing brain energy balance. Mounting evidence reveals that fluctuations in metabolic rates correspond to disparate cognitive and behavioral modes - quiescent *vs.* activated states^[9]. During synchronized neuronal operations, augmented demand for, as well as consumption of, oxygen and glucose ensues, collectively termed neurovascular and neurometabolic coupling. Integral players mediating this symphony of metabolic equilibrium maintenance are none other than glial cells, especially astrocytes, which occupy key positions in this complex regulatory network^[10].

There is a growing body of research bolstering the hypothesis that disruptions in energy metabolism play a central role in the onset and advancement of neurological disorders. The present understanding concerning disrupted regional energy expenditure tied to neurodegenerative disorders is consolidated in [Table 1](#)^[11-16]. Regional biochemical adaptations imply the significant impact of locally transformed microenvironments accompanying neurodegeneration^[2]. Acting as a focal participant birthed from manifold metabolic avenues, reactive oxygen species (ROS) meaningfully add to this detrimental local environment. ROS have been identified as increasingly prevalent in the mammalian central nervous system during aging^[17]. Mitochondria are among the primary sources of ROS, generating it through oxidative phosphorylation. Normally, ROS participates in physiological functions like inflammation and synaptic plasticity^[18]. Nevertheless, an excess production of ROS within cells can trigger oxidative stress, disrupting redox homeostasis and resulting in mitochondrial dysfunction. This chain reaction could potentially exacerbate age-related neurological disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), as supported by animal research findings^[17,19]. Studies have reported significant reductions in ATP synthesis capacity, pyruvate dehydrogenase activity, and calcium buffering abilities in aged animals compared to their younger counterparts^[20]. Recent investigations also emphasize the impact of mitochondrial damage induced by ROS on several neurodegenerative illnesses, underscoring the critical significance of energetic malfunctions^[21]. Accompanying diminished ATP generation, the amassed ROS foster a markedly proinflammatory setting. Within the aged brain, neurons endure prolonged exposure to this persistent inflammatory atmosphere, conceivably heightening neuronal loss and synaptic abnormalities, thus facilitating the evolution of the senescent brain toward pathological manifestations.

Table 1. The brain regions associated with abnormal glucose metabolism in neurodegenerative diseases

Disorders	Metabolic change	Related brain area	Ref.
AD	Glucose hypometabolism	Posterior cingulate cortex; precuneus; anterior hippocampus; parahippocampal gyrus	[11,12]
PD	Glucose hypometabolism	Premotor; parieto-occipital cortex	[13]
	Glucose hypermetabolism	Cerebellum; pons; paracentral gyrus; lentiform nucleus	
HD	Glucose hypometabolism	Frontal lobe; temporal lobe; striatum	[14]
ALS	Glucose hypometabolism	Prefrontal; cingulate cortex; caudate nuclei; rolandic operculum; thalamus	[15,16]
	Glucose hypermetabolism	Amygdalae; midbrain; pons; cerebellum	

AD: Alzheimer’s disease; PD: Parkinson’s disease; HD: Huntington’s disease; ALS: amyotrophic lateral sclerosis.

Considering the substantial involvement of glial cells in shaping and managing the central nervous system’s microenvironment, it is logical to posit that the energy metabolic condition of these cells plays an essential role in the shift from health to disease. Indeed, reactivated astrocytes have emerged as a prominent source of ROS; despite primarily utilizing glycolysis for ATP production, they generate considerable quantities of mitochondrial ROS^[22]. These accumulating astrocyte-derived ROS have downstream consequences on neuronal activity and animal behavior^[23]. Additionally, it has been extensively established that astrocytes govern cerebral blood flow by fine-tuning the diameter of microvasculature, consequently modulating the delivery of both oxygen and glucose. In terms of other glial subtypes, microglia - given its intimate connection to the central nervous system’s inflammatory responses - have shown close ties between metabolic reprogramming and polarization^[24]. Glial cells not only construct the microenvironment but are themselves influenced by variations in the metabolic landscape; their functional capabilities and survivability remain subject to these modifications^[6]. For instance, the aged brain faces challenges related to the insufficient provision of energy substrates due to compromised local microcirculation, which can fundamentally transform glial cell metabolism, eventually inflicting detriment upon the integrated neuronal circuitry. Nevertheless, the ramifications of modified glial energy metabolism on brain aging and attendant diseases remain an active area of rigorous investigation.

In this review, we will provide a concise overview of established concepts while delving into recent advancements on three key topics: (1) The distinctive characteristics of glial energy metabolism in the central nervous system; (2) The metabolic alterations occurring in glial cells within the aging brain; (3) The impact of metabolic reprogramming in glial cells on neurodegeneration, particularly in PD. Our aim is to offer deeper insights into the association between dysfunction in glial energy metabolism and brain disorders, thereby illuminating the potential for novel therapeutic strategies centered around modulating glial metabolic states.

GLIA ENERGETICS AND THE NORMAL FUNCTION OF THE CENTER NERVE SYSTEM

In recent decades, there has been increasing focus on the study of glial energy metabolism, considering the distinct morphologies and functions of the three major subtypes of glial cells: astrocytes, microglia, and oligodendrocytes. While some similarities exist in their bioenergetic characteristics, each subtype serves different neuronal functions. For instance, both astrocytes and oligodendrocytes favor glycolysis and provide bioenergetic support to neurons^[6,25]. However, oligodendrocytes primarily facilitate the propagation of action potentials and maintain a close relationship with axonal mitochondria^[26], whereas the energy demands of synaptic transmission are more closely associated with astrocytes^[27]. Undeniably, the harmonious bioenergetic collaboration between various glial cells and neurons forms an integral pillar upholding regular brain functions in humans [Figure 1].

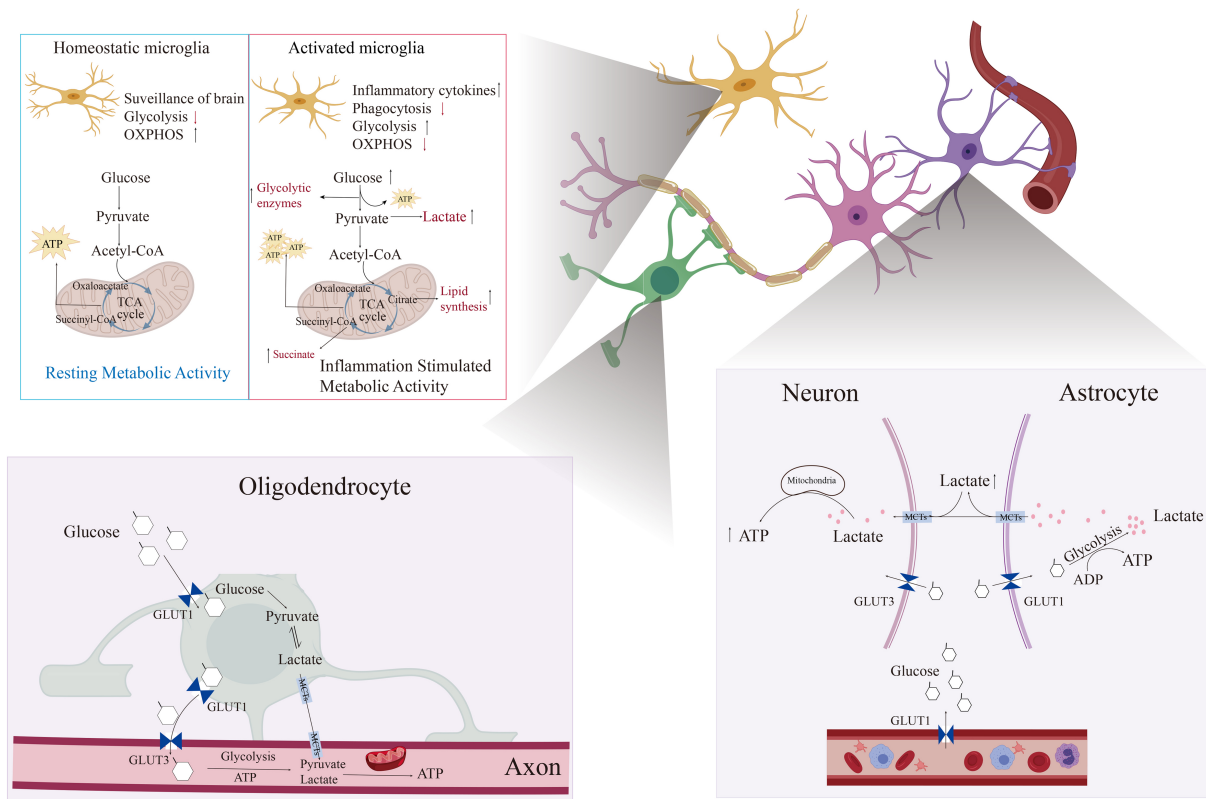


Figure 1. The metabolic types of normal nerve cells.

While it has been reported that oligodendrocyte dysfunction and demyelination may contribute to neuronal death in neurodegenerative diseases^[28], particularly AD^[29], our current understanding of oligodendrocyte metabolic dysfunctions and their impact on the degeneration of the nigrostriatal pathway remains limited. Therefore, our discussion will primarily focus on astrocytes and microglia, examining their metabolic dysregulations in aging and degenerative brain conditions. We anticipate that future studies will provide deeper insights into oligodendrocyte metabolism and its role in neurodegeneration.

In physiological conditions, distinct metabolic profiles characterize different subtypes of brain cells to facilitate their respective functions. Neurons predominantly utilize mitochondrial oxidative phosphorylation, whereas astrocytes predominantly engage in aerobic glycolysis. Additionally, astrocytes metabolize glucose into lactate, which serves as a crucial metabolic substrate for neurons. Oligodendrocytes primarily rely on glycolysis, and the energy metabolism of microglial cells undergoes reprogramming in response to their specific states.

Normal bioenergetic characteristics of astrocytes

Comprising the majority of glial cells constituting the brain, astrocytes fulfill indispensable metabolic obligations benefitting neighboring neurons. Astrocytes possess distinctive cellular structures and occupy strategic positions that enable them to perceive environmental cues and adapt to associated fluctuations^[6]. Positioned within the neurovascular unit, astrocytes consistently mediate the interface between neurons and capillaries. Their end feet establish connections with both blood vessels and synapses, fostering intricate interactions among these integral components^[30]. Recently, Nippert *et al.* proposed that astrocytes can facilitate the increase in cerebral blood flow triggered by hypoglycemia via a calcium-dependent mechanism

involving the release of vasodilators^[31]. Their study employed insulin-treated mice to simulate hypoglycemia conditions. Under hypoglycemic conditions, arterioles undergo dilation, concomitant with heightened astrocytic Ca^{2+} signaling. Application of specific inhibitors targeting the production of astrocyte-derived vasodilators, such as prostaglandin and epoxyeicosatrienoic acids, resulted in substantial reductions of arterial dilation by 89% and 76%, respectively^[31]. This observation suggests a potential mechanism by which astrocytes modulate cerebral blood flow to facilitate glucose transport from blood vessels to astrocytes, thereby generating metabolic substrates crucial for supporting neuronal activity.

Current research indicates that under normal circumstances, astrocytes primarily utilize glucose for energy production. Glucose is taken up into the cell via glucose transporter (GLUTs) proteins, particularly GLUT1, and is phosphorylated by hexokinase (HK) to form glucose-6-phosphate^[32]. This glucose can then enter various metabolic pathways, including glycolysis, the pentose phosphate pathway (PPP), OXPHOS, and glycogen synthesis^[33]. However, astrocytes predominantly metabolize glucose through aerobic glycolysis, which not only meets their lower energy demands but also produces lactate, a metabolic substrate crucial for neuronal support. As early as 1994, Pellerin *et al.* proposed the astrocyte-neuron lactate shuttle hypothesis^[34]. The process through which lactate shuttles between neurons and astrocytes is as follows: following neuronal stimulation, adjacent astrocytes can uptake excess glutamate at the synapse. Subsequently, the entry of sodium into astrocytes activates Na^+/K^+ ATPase, the activation of which consumes ATP produced by glycolysis. Lactate produced by glycolysis is transported extracellularly by monocarboxylate transporters (MCT1 and MCT4), and then transported into neurons via MCT2 on the neuronal membrane, providing oxidative phosphorylation substrates for neurons^[35,36]. Roumes *et al.* developed a rat model where they specifically downregulated cortical neuronal MCT2 or astrocytic MCT4. They then measured metabolic and hemodynamic responses to sensory stimulation using functional magnetic resonance spectroscopy and blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI)^[37]. Their results convey that the shuttle of lactate between astrocytes and neurons is indispensable for neuro-metabolic and neurovascular coupling. Furthermore, recent research by Muraleedharan *et al.* found that adenosine monophosphate-activated protein kinase (AMPK) is a key enzyme regulating the production of lactate by astrocytes and its transfer to neurons^[38]. They generated AMPK-KO astrocytes *in vitro* and cultured them in a medium containing $[\text{U}-^{13}\text{C}]$ glucose. The results showed that AMPK-KO astrocytes exhibited a 50% reduction in lactate production, along with significantly decreased glucose uptake and membrane translocation of the glucose transporter GLUT1. However, the addition of lactate or wild-type astrocytes to the culture medium restored these functions. In animal experiments, the researchers found that the lactate content in the brains of AMPK knockout mice on postnatal day 28 decreased by 40% as measured by ^1H magnetic resonance spectroscopy. Additionally, cortical thinning and neuronal loss were observed in these mice^[38]. These findings underscore the importance of AMPK-regulated glycolytic metabolism in astrocytes for maintaining neuronal homeostasis.

Metabolic processes of lipids are intricately linked to energy production in astrocytes^[39]. While neurons have limited lipid metabolism capabilities, astrocytes exhibit robust lipid metabolism enzyme activity, necessitating a high energy supply^[40]. Astrocytes synthesize cholesterol in the brain and transport it via ApoE-containing lipoproteins^[41]. Neurons absorb lipids derived from astrocytes to support synaptic formation and function^[42]. When neurons become hyperactive, they produce peroxidized lipids, raising questions about how neurons manage lipid accumulation. Recent research has shed light on this process: hyperactive neurons generate toxic fatty acids (FAs), which are transferred to astrocytes via ApoE-positive lipid droplets. Astrocytes then metabolize FAs through mitochondrial β -oxidation and initiate detoxification gene expression programs^[43]. This result highlights the dynamic interplay between neurons and astrocytes in maintaining brain lipid homeostasis. Hence, it becomes entirely justifiable to propose that

impairment in astrocytic energy metabolism would likely compromise neuronal function and viability, given its adverse implications on lipid processing.

Microglia has distinct metabolic patterns in normal brain

Microglia serve as the central nervous system's resident macrophages, maintaining homeostasis throughout brain development and adulthood^[44]. They exhibit high plasticity, enabling them to adapt to diverse environmental cues through extensive phenotypic remodeling while surveilling the brain milieu^[45]. This adaptability is closely linked to their ability to utilize various energy substrates, such as glucose, lipids, ketone bodies, lactate, and pyruvate^[46,47]. Unlike astrocytes, microglia primarily rely on oxidative phosphorylation for ATP production using glucose^[48]. FAs undergo ATP production by coupling with peroxisomes to generate acetyl-CoA, which then enters the tricarboxylic acid (TCA) cycle^[49]. In their activated state, however, macrophages display diverse metabolic phenotypes. When stimulated by lipopolysaccharide (LPS), proinflammatory macrophages demonstrate heightened glycolytic metabolism alongside compromised mitochondrial oxidative phosphorylation^[50,51]. Conversely, anti-inflammatory macrophages induced by interleukin 4 (IL-4) exhibit elevated mitochondrial oxidative phosphorylation^[52]. The metabolic alterations of both astrocytes and microglia are depicted in [Figure 2](#).

Astrocytes and microglia exist in two distinct states: resting and activated. In the resting state, astrocytes predominantly rely on glycolysis for energy production. However, upon activation, they primarily depend on OXPHOS. Microglia, on the other hand, exhibit a different metabolic profile. In their resting state, microglia primarily utilize OXPHOS to generate ATP from glucose. However, upon activation, their metabolic patterns vary depending on their physiological functions. Anti-inflammatory microglia show an increase in mitochondrial oxidative phosphorylation. Conversely, in proinflammatory microglia, there is an upregulation of glycolytic metabolism, while mitochondrial oxidative phosphorylation is impaired. Proinflammatory microglia are characterized by a rounded morphology, indicative of their hyperactive state, whereas anti-inflammatory microglia exhibit an elongated morphology.

Microglia possess crucial properties such as phagocytosis and inflammation. They play a significant role in synaptic pruning through phagocytosis, which fosters synapse formation and development, while also maintaining a normal neuronal count in the developing brain^[53]. In pathological conditions like pathogen infections or acute ischemic strokes, microglia release cytokines and chemokines, such as interleukin-1 beta (IL-1 β) and chemokine (C-X-C motif) ligand 1 (CXCL1), to safeguard the central nervous system by recruiting neutrophils^[54,55]. A growing body of evidence suggests that altering the metabolism of microglia directly influences their phagocytic and inflammatory responses. In terms of inflammation, microglia can detect changes in brain metabolism and adjust their own metabolic processes to regulate neuronal activity. For instance, fluctuations in blood glucose levels have been linked to the inflammatory activation of microglia and an increased secretion of proinflammatory factors^[56]. It is noteworthy that recent investigations utilizing single-cell RNA sequencing and spatial transcriptomic analysis have provided new insights into microglial subtypes. The traditional classification of microglia into proinflammatory (M1) and anti-inflammatory (M2) subtypes is now considered oversimplified^[57]. More complex subtypes of microglia have been identified under specific conditions associated with distinct neurodegenerative disorders^[57]. The extent to which metabolic plasticity contributes to the divergence of reactive microglia remains to be further studied.

Microglia not only possess metabolic plasticity but also engage in metabolic interactions with neurons. Triggering receptor expressed on myeloid cells 2 (Trem2), a myeloid cell-specific gene expressed in brain microglia, has been shown to regulate neuronal development by influencing the metabolic fitness of

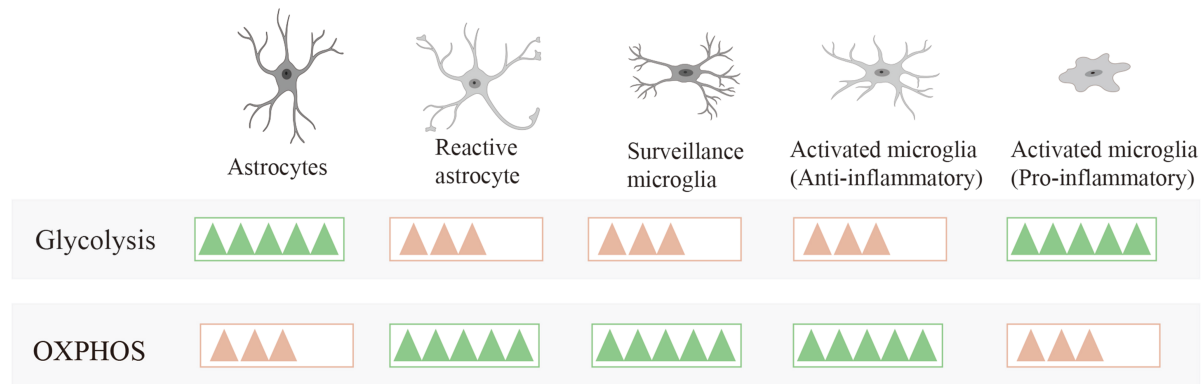


Figure 2. The energy metabolism patterns of astrocytes and microglia in different states.

neurons in a region-specific manner^[58]. Additionally, microglia may monitor and protect neurons by sensing changes in mitochondrial energy at the microglia-neuron somatic junction^[59]. Impairment in mitochondrial dynamics is associated with pathological processes in neurodegenerative diseases like AD and PD^[60]. Microglial metabolic plasticity also responds to metabolic changes in the brain and body. Glial-neuronal interactions form a circuit that senses internal signals and adjusts behavior and metabolism according to metabolic states^[61]. For instance, obesity, an energy metabolism disorder, induces brain inflammation and activates microglia, contributing to cognitive impairment by aberrantly phagocytosing synaptic spines. However, the precise mechanisms underlying microglial activation during obesity remain incompletely understood^[62].

ALTERED CELLULAR ENERGY METABOLISM IN THE AGING BRAIN

As humans age, notable structural remodeling occurs within the brain, a phenomenon readily detectable through computed tomography and magnetic resonance imaging modalities^[63,64]. Prominent examples include the observable decreasing trends observed in both gray matter volume and white matter volume over time. A previous investigation revealed a significant reduction in the overall gray matter volume of the brain, with particularly pronounced atrophy noted in the frontal and temporal lobes^[65]. This decrease in gray matter volume is closely linked to the deterioration of cognitive functions. For instance, the atrophy of gray matter in the prefrontal lobe correlates with a decline in executive function^[66]. In contrast to gray matter, the alterations in white matter during the aging process exhibit distinct patterns. The integrity of white matter structure undergoes dynamic changes with age, showing a gradual increase before age 40, peaking around 50 years, and subsequently declining after 60 years^[67]. Furthermore, the age-related deterioration in cognitive functions is closely linked to alterations in white matter structural integrity, which are implicated in neurodegenerative conditions. Subclinical mild cognitive impairment may elevate the susceptibility to developing such diseases because of these changes^[68]. The alterations in brain structures can be attributed primarily to neuronal cell loss and impaired glial function. Given the critical functions of energy metabolism in maintaining central nervous system homeostasis, it is unsurprising that close connections exist between macroscale structural alterations in the brain and microscale functional modifications to cellular metabolic reprogramming^[69-71].

Metabolic reprogramming of aging neuron

Progressing age engenders disruptions in neuronal energy metabolism, crystallized along two primary dimensions: (1) anomalous glucose usage patterns; and (2) compromised mitochondrial oxidative phosphorylation^[72,73]. Age-induced insulin resistance, accompanied by deficient glucose transportation,

materializes within neuronal communities, yielding substantially curtailed glucose uptake. According to a longitudinal population-based investigation, the incidence of insulin resistance correlates adversely with escalating cognitive deterioration throughout the aging journey^[72]. Yarchoan *et al.* uncovered analogous outcomes after analyzing postmortem brain samples sourced from geriatric subjects, wherein elevated levels of serine 312 phosphorylated insulin receptor substrate 1 (IRS-1) were noted, suggesting enhanced insulin resistance^[74]. This was paralleled by reduced neuronal glucose assimilation capacities. Over and above external determinants (e.g., hormonal imbalance), internally driven elements, specifically dysregulated glucose ingress attributable to lost GLUT3 transporters, encumber optimal neuronal metabolic efficiency as years accrue^[75]. Thus, during aging, declines in both extrinsic (endocrine irregularities) and intrinsic components (neuronal nutrient absorption) potentiate diminished neuronal glucose metabolic efficiencies.

On the other hand, neuronal energy provision primarily relies on mitochondrial oxidative phosphorylation, underscoring the pivotal role of mitochondria in maintaining neuronal energy balance. Mitochondria are distributed throughout both axons and dendrites, serving to generate ATP for sustaining electrochemical neurotransmission, cellular upkeep, and repair processes, crucially supporting the heightened energy demands of axonal activity^[76,77]. Nonetheless, aging renders axons particularly vulnerable to its effects, affecting energy metabolism through various mechanisms^[78]. Firstly, with aging, there are discernible changes in both the quantity and morphology of mitochondria within axons. Vagnoni *et al.* observed a significant decrease in mitochondrial transport within the axons of fruit fly wing neurons during aging^[73]. In advanced mice, the volume and length of individual mitochondria within the axons of the optic nerve notably increase^[79]. Secondly, aging contributes to heightened hyperexcitability in cortical networks, consequently escalating the energy requirements for axonal propagation of action potentials and synaptic neurotransmitter release^[80,81]. Furthermore, it is imperative to recognize that the elongation of axons reduces energy availability at their distal ends, a factor of significance in long-distance projections like the nigrostriatal pathway, implicated in PD.

Bioenergetic shifts of glial cells in aging brain

As previously discussed, the maintenance of normal neuronal activity relies on the efficient metabolic coordination between neurons and glial cells, with particular emphasis on the metabolic support provided by astrocytes. However, recent research indicates that aging is associated with a decline in glycolysis and an augmentation of mitochondrial oxidative metabolism in astrocytes^[82,83]. Utilizing magnetic resonance spectroscopy to investigate mitochondrial metabolism in both neurons and astrocytes, a recent study revealed that, compared to younger individuals, the elderly population demonstrates diminished neuronal mitochondrial metabolism but heightened astrocytic mitochondrial metabolism within the brain^[84]. The age-related metabolic transition observed in astrocytes could potentially jeopardize lactate production, consequently restricting the fuel supply available for neuronal OXPHOS. It is noteworthy that alterations in the intrinsic state of astrocytes, characterized by their transition into reactive astrocytes, induce changes in their energy metabolism profile^[85]. In studies conducted on rodent models, researchers isolated primary cortical astrocytes from rats aged 7, 13, and 18 months. They observed age-associated shifts in the metabolic pathways of these cells, transitioning from glycolysis to mitochondrial oxidative phosphorylation, accompanied by elevated levels of reactive astrocytes [Figure 2]^[86]. These results suggest that the increased mitochondrial oxidative phosphorylation may promote a functional shift in astrocytes from a neuro-supportive state to a neurotoxic state. However, recent research has presented contrasting findings. McNair *et al.*, employing stable isotope tracing *in vitro*, observed a significant reduction in astrocytic TCA cycle activity and oxidative phosphorylation metabolism in hippocampal slices of aged mice. Conversely, glycolytic activity and glutamate uptake exhibited a notable increase^[87]. These findings suggest a hypothesis that aging could potentially impact the metabolic energy pathways of distinct subpopulations of astrocytes differently across various brain regions^[88].

Among all brain cells, astrocytes serve as the primary sites for FA oxidation, and with brain aging, there is an observed increase in the utilization rate of free FAs^[40]. Research by Boisvert *et al.* revealed a significant reduction in the expression of cholesterol synthesis genes in astrocytes of aged mouse brains compared to adult mice, indicating a shift in lipid metabolism in these cells^[39]. Subsequent studies have demonstrated that during aging, astrocytes not only experience a decline in glycolytic capacity, impeding the effective provision of necessary energy substrates for neurons, but also exhibit an increase in FA oxidation, resulting in the production of acetyl-CoA, thereby further modulating mitochondrial metabolic functions^[83]. This mechanism may contribute to the transition of astrocyte function from a resting to a reactive state.

Age-dependent metabolic reprogramming also affects microglial cells. Research by Mela *et al.* revealed that in the brains of elderly animals, microglial cells exhibit significantly elevated glycolysis levels and adopt a proinflammatory phenotype^[89]. This underscores that the glucose metabolism activity of microglial cells is not only influenced by intrinsic changes but also undergoes metabolic reprogramming with advancing age. Evidently, the regulatory mechanism involving proinflammatory prostaglandin E2 (PGE2) signaling stands out as a potential candidate controlling the age-associated shift in microglial energy metabolism. Mechanistically, engagement between PGE2 and its cognate EP2 receptor prompts glucose routing into glycogen reserves, leading to activation of the protein kinase B (AKT)-glycogen synthase kinase 3 beta (GSK3 β)-glycogen synthase 1 (GYS1) cascade; this eventuality suppresses incoming glucose fluxes destined for mitochondrial OXPHOS, thereby indirectly reducing ATP yields. Quite remarkably, amplified PGE2 signaling triggers direct reconfiguration of aged microglia, shifting them away from customary anti-inflammatory tendencies toward embracing a decidedly proinflammatory phenotype instead^[90].

Furthermore, in addition to glucose metabolism, aging also impacts the lipid metabolism of microglial cells. Recent investigations have identified a notable increase in apolipoprotein E (APOE) mRNA expression within isolated microglial cells from aged mice^[91,92]. Dysregulation of APOE has been linked to the formation of lipid droplets. Victor *et al.* demonstrated that microglial cells derived from induced pluripotent stem cells of individuals carrying APOE risk variants display abundant lipid droplets (LD)^[93]. Transcriptomic analysis of lipid droplet-associated microglia unveiled severely compromised phagocytic activity in microglial cells, accompanied by heightened production of ROS and inflammatory cytokines, exhibiting characteristics partially mirroring those of lipopolysaccharide-treated mouse microglia^[94]. Recent studies have also demonstrated that lipid-laden microglia in the aged brain exhibit exacerbated innate immune responses to stroke^[95]. However, further investigation is required to elucidate the crosstalk between altered lipid metabolism and shifts in energy production patterns in aged microglia.

DYSREGULATED GLIAL ENERGY METABOLISM IN PD

PD represents the second most common neurodegenerative disorder worldwide, characterized by the selective loss of dopaminergic (DA) neurons in the midbrain. Despite extensive associations drawn between PD-linked DA neuronal death and α -synuclein, along with several influential factors, the precise molecular machinery of such lethal neurodegeneration remains elusive. Unquestionably, given the exceedingly high energy demands imposed upon the nigrostriatal system, it seems plausible that aging-associated energy failures might critically contribute to PD-associated neurotoxicity. Indubitably, numerous lines of evidence point convincingly toward pervasive bioenergetic defects embedded within the PD pathophysiology.

Dysfunctions of energy metabolism in dopaminergic neurons

Advanced age serves as a recognized risk factor for developing PD. Even in the absence of PD, the aging brain experiences gradual depletion of DA neurons located in the substantia nigra zona compacta (SNc), reaching approximately 30%-40%^[96]. However, once afflicted with PD, the extent of DA neuronal loss in the

SNc often surpasses 80%^[97]. Morphologically speaking, residual healthy DA neurons display signs of hypertrophy during typical aging, whereas those affected by PD demonstrate marked atrophy^[98]. Further exploration conducted by researchers such as Elstner *et al.* aimed to distinguish any discrepancies in gene expression changes exhibited by dopaminergic neurons between aging and PD cases. Utilizing laser capture microdissection, they extracted DA neurons from the SNc of PD patients and non-PD controls, followed by comparative expression profiling and subsequent pathway analyses. Findings indicated that PD-impacted DA neurons expressed genes strongly associated with mitochondrial dysfunction and profound energy metabolic distress^[99]. Additional parallel observations made by Keeney *et al.* highlighted comparable perturbations in the SNc of PD brains, whereby impairment of electron transport chain (ETC) Complex I activity resulted in overwhelmingly increased production of ROS^[100] and severe hindrances to proper ATP synthesis^[101,102]. Collectively, these discoveries highlight the striking correlation existing between DA neuronal mortality in the SNc and underlying metabolic disturbances.

The higher energy demands of DA neurons can be attributed to their unique physiological characteristics^[103]. Recent perspectives suggest that the activation of SNc DA neurons relies on a specific type of L-type voltage-gated calcium ion channel, facilitating calcium ion efflux that is ATP-dependent^[104]. Moreover, SNc DA neuron axons are relatively large, primarily relying on oxidative phosphorylation for energy supply, resulting in higher levels of ROS at their axon terminals^[103]. Additionally, SNc DA neurons exhibit another two distinct properties, which make them more vulnerable to bioenergetic dysregulation than other neurons: (1) Dopamine can produce the derivative tetrahydroisoquinoline (TIQ), which, in combination with methylglyoxal - a significant byproduct of glucose metabolism - forms 1-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (ADTIQ), contributing to the degeneration of DA neurons^[105]; (2) They contain elevated levels of iron, which can exacerbate oxidative stress, triggering the conversion of α -synuclein from an α -helix to a β -sheet conformation. This transformation promotes α -synuclein aggregation, thereby increasing the pathological risk of PD^[106]. Growing evidence suggests that metabolic abnormalities in PD may contribute to disease progression by promoting α -synuclein aggregation. Hyperglycemia has been shown to influence the aggregation of α -synuclein, potentially impairing neuronal glycolytic capacity^[107]. Metabolic dysfunctions in PD patients involve not only impaired glucose metabolism but also abnormalities in lipid metabolism. Altered lipid metabolism is closely associated with α -synuclein as well. For instance, oleic acid can induce the formation of α -synuclein aggregates in human neuronal cells^[108]. A recent study identified a class of lipid molecules, specifically lysophosphatidylcholine (LPC), that selectively recognize and stabilize the monomeric form of α -synuclein. This research highlights LPC's critical role in maintaining the natural conformation of α -synuclein and preventing its pathological aggregation, thus linking lipid metabolism disturbances to α -synuclein pathology in PD^[109].

Although research evidence from patient studies suggests a close association between disrupted energy metabolism and PD, it remains uncertain whether bioenergetic dysfunction precedes or results from neuronal degeneration. Data from PD animal models may shed light on this inquiry. We summarized metabolic disruptions observed in several chemically induced and genetically engineered models in [Table 2](#)^[110-120]. Intriguingly, whether a Parkinson-like phenotype is induced by neurotoxic compounds or genetic factors, mitochondrial dysfunction emerges as a crucial pathogenic mechanism^[110,111]. The escalation in ROS closely correlates with metabolic shifts from mitochondrial OXPHOS to glycolysis. Perhaps, under the compounded stress of disease and aging, prolonged oxidative stress in the brain leads to irreversible mitochondrial damage, hindering compensatory glycolysis increases. Whether preserving or restoring mitochondrial function in neurons emerges as a prospective PD treatment strategy, awaiting further validation.

Table 2. The energy metabolism alternations in different PD models

PD model	Gene/compound	Metabolic change	Ref.
Chemical models	MPP ⁺	Mitochondrial respiration↓ Glycolysis↑	[110]
	Rotenone	Pentose phosphate pathway↑ Glycolysis↓ Mitochondrial respiration↓	[112]
	6-OHDA	Glycolysis↑	[113,114]
	Paraquat	Pentose phosphate pathway↑ Glycolysis↓ Mitochondrial respiration↓	[114]
Genetic models	α -Synuclein	Lipid metabolism alteration Mitochondrial respiration↓	[111,115,116]
	Parkin; DJ-1; LRRK2; PINK1	Glycolysis↑ Mitochondrial respiration↓	[117-120]

PD: Parkinson's disease; MPP⁺: 1-methyl-4-phenylpyridinium; 6-OHDA: 6-hydroxydopamine.

Bioenergetic disruptions of glial cells in PD brain

Investigations centered on both patient populations and relevant genomic animal models reveal that many PD-linked mutated genes indeed find expression within astrocytes, influencing their energy metabolic landscapes accordingly^[32]. Table 3 provides a condensed overview detailing the range of astrocytic energy metabolic traits germane to familiar PD pathogenic gene variants^[121-127]. Remarkably, divergent pathogenic genes exhibit varying degrees of disruption to astrocytic energy homeostasis, with mutant α -synuclein playing a significant role in bioenergetic deregulation. Once internalized by astrocytes, mutant α -synuclein impairs lipid catabolism by reducing the metabolic turnover rates of arachidonic acid and palmitic acid, thereby skewing cellular energy balance^[128,129]. Furthermore, α -synuclein intervention can impede the proper localization of aquaporin-4, undermining efficient glutamate uptake and leading to abnormal glutamate metabolism^[124].

Recent research conducted by Sonninen *et al.* has revealed that in PD, alterations in astrocytic metabolism primarily stem from changes in mitochondrial function^[127]. Utilizing induced pluripotent stem cells (iPSCs) derived from PD patients and subsequent differentiation into astrocytes, they observed notable shifts. Specifically, both maximal and spare respiratory capacities of astrocytes were significantly diminished, accompanied by a marked attenuation in glycolysis. Additionally, analysis of mitochondrial DNA (mtDNA) indicated lower levels in astrocytes from PD patients. These findings were corroborated by Russ *et al.*, who exposed human astrocytes to α -synuclein fibers, demonstrating a significant reduction in mitochondrial respiration within astrocytes^[130]. Under conditions of aging, there is a decrease in glycolysis and an increase in oxidative phosphorylation within astrocytes. Conversely, in PD, both glycolysis and oxidative phosphorylation significantly decrease due to mitochondrial damage and reduced glucose uptake. Consequently, we propose a hypothesis: under normal circumstances, astrocytes predominantly rely on glycolysis for energy production, but as the organism ages and encounters heightened inflammation and oxidative stress, they transition toward mitochondrial oxidative phosphorylation to meet energy demands. This metabolic shift serves multiple purposes, including sustaining astrocytic energy requirements, facilitating the conversion of toxic substances like excitatory glutamate, and bolstering antioxidant capacity such as glutathione synthesis. However, in PD, dysfunctional mitochondrial metabolism in astrocytes compromises energy support, antioxidant function, and detoxification processes. Therefore, disruptions in mitochondrial metabolism may act as a pivotal “switch” in the metabolic reprogramming of astrocytes in PD. It is noteworthy that there are two subtypes of astrocytes in the substantia nigra pars compacta, namely protoplasmic astrocytes and fibrous astrocytes. However, studies suggest that only protoplasmic astrocytes contribute to the accumulation of mutated α -synuclein^[131].

Table 3. The energy metabolism characteristics of astrocytes associated with various PD mutations

Mutated genes	Characteristics of metabolic perturbations	Ref.
<i>PARK7</i>	Glutamate uptake↓ Lipid raft assembly↓ Mitochondrial function↓	[121,122]
<i>SNCA</i>	Glutamate uptake↓ TAG↑ Lipid raft assembly↓	[123,124]
<i>PINK1</i>	ATP production↓ Oxygen consumption↓ ROS↑ Lipid raft assembly↓	[125]
<i>PARK2</i>	Glycolysis↓ Lipid raft assembly↓	[126]
<i>LRRK2</i>	Glycolysis↓ OXPHOS↓ Lipid raft assembly↓	[127]

PD: Parkinson's disease; TAG: triacylglycerol; ATP: adenosine triphosphate; ROS: reactive oxygen species; OXPHOS: glycolysis and oxidative phosphorylation.

The energy metabolic reprogramming in the PD brain not only contributes to the demise of DA neurons but may also play a role in the emergence of non-motor symptoms. Our recent research indicates that there is a repression in mitochondrial transcription and function in cortical astrocytes of PD brain, coinciding with the activation of the hypoxia-inducible factor (HIF) pathway. This disruption in energy production within cortical astrocytes could worsen the dysfunction of the neuronal network responsible for mood regulation, potentially triggering the onset of depression associated with PD^[132]. Previous studies have often focused on the switch from glycolysis to OXPHOS in disease-related astrocytes. However, our results underscore the importance of mitochondrial energy production and its role in regulating key gene expressions. Interestingly, our study also reveals distinct response patterns of cortical astrocytes to PD-associated neurodegeneration compared to midbrain astrocytes, potentially due to differences in energy metabolic signaling. Although the underlying mechanisms require further investigation, our findings emphasize the importance of studying the region-specific bioenergetics of astrocytes in PD and other neurodegenerative diseases^[132].

The molecular regulators of metabolic reprogramming, which are crucial for developing novel therapeutic strategies, however, remain largely unknown. One of the key regulatory pathways is the WNT/ β -catenin signaling pathway, implicated in many neurodegenerative diseases^[133]. Vallée *et al.* investigated the thermodynamic implications of metabolic reprogramming in PD, discovering a downregulation of WNT/ β -catenin signaling and its involvement in the brain hypometabolism observed in PD patients. They propose that in PD, the thermodynamic behavior of metabolic enzymes is altered due to dysregulation of the WNT/ β -catenin pathway. For example, downregulation of this pathway leads to the inactivation of glycolytic enzymes such as Glut, pyruvate kinase M2 isoform (PKM2), pyruvate dehydrogenase kinase 1 (PDK1), and monocarboxylate transporter 1 (MCT-1), resulting in decreased metabolism, oxidative stress, and cell death^[134]. Furthermore, it has been reported that the crosstalk between midbrain DA neurons and astrocytes is regulated by the Frizzled-1/ β -catenin signaling pathway, modulated by WNT1^[135]. However, the precise role of the WNT/ β -catenin signaling pathway in glial metabolic reprogramming remains under investigation. Additionally, the involvement of other signaling pathways in the metabolic dysregulation observed in neurodegenerative diseases is still being explored.

The excessive activation of microglial cells plays a pivotal role in the progression of PD. Activated microglial cells are previously categorized into M1 and M2 phenotypes. These phenotypes exhibit distinct metabolic patterns in response to various environmental stimuli, enabling them to fulfill their respective functions^[136]. In the PD brain, microglia are activated by several factors, including damage-associated molecular patterns (DAMPs) released by dying neurons, proinflammatory factors from astrocytes, and extracellular α -synuclein oligomers^[137]. These stimuli promote the activation of M1 microglial cells, triggering neuroinflammation and leading to the loss of dopaminergic neurons^[138]. In a recent study, Lavis *et al.* directly observed activated microglial cells and elevated levels of proinflammatory factors in the brains of PD patients using [¹⁸F]-DPA714 TSPO positron emission tomography (PET) imaging^[139]. The primary inquiry revolves around delineating the alterations in energy metabolism within microglial cells in PD. The bulk of evidence addressing this question stems from studies conducted on animal or cell-culture models of PD. Researchers have identified metabolic reprogramming in microglial cells of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, characterized by a transition from oxidative phosphorylation to aerobic glycolysis, accompanied by an upsurge in proinflammatory responses^[140]. Additionally, both *in vivo* and *in vitro* PD models have demonstrated heightened activity of glucose-6-phosphate dehydrogenase within the pentose phosphate pathway, leading to the accumulation of ROS and subsequent neuronal damage^[141].

The metabolic reprogramming of microglial cells entails intricate modulation involving multiple signaling pathways and cytokines. Firstly, *in vitro* experiments have revealed a significant elevation in the mRNA levels of PKM2, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and GLUT1, alongside increased lactate production, following α -synuclein treatment of microglial cells^[142]. This highlights that there are changes in the glucose metabolism of activated microglial cells. Secondly, upon activation of microglial cells, hypoxia-inducible factor 1 alpha (HIF-1 α) stimulates the targets of rapamycin (mTOR), leading to the upregulation of glycolytic enzymes^[143,144]. Previous studies have also found that in a mouse model of PD, microglia induce metabolic reshaping (transition from oxidative phosphorylation to aerobic glycolysis) through the mTOR/HIF-1 α pathway, thereby exacerbating the pathophysiological phenotype of PD^[145]. Consequently, the mTOR/HIF-1 α pathway emerges as a promising targeted regulatory axis for modulating these metabolic alterations. Notably, the mTOR signaling pathway exerts a multifaceted regulatory role encompassing glucose, lipid, and other metabolic pathways, thereby influencing mitochondrial function and dynamics^[146]. This suggests that metabolic reprogramming of microglial cells in the context of PD may involve multiple metabolic processes.

In addition to glucose metabolism, there is a growing focus on changes in the lipid metabolism of microglia in PD. Researchers have observed lipid accumulation in microglial cells in both animal models and PD patients, which, along with microglial cell damage, contributes to neuroinflammation and disruptions in neural circuits^[147]. This suggests a potential pathogenic mechanism of microglial cells in PD progression. However, understanding of the mechanisms underlying microglial cell lipid metabolism and PD progression remains limited. Hence, further research is necessary to elucidate the metabolic characteristics of microglial cells in PD, facilitating more effective treatment and prevention strategies.

Metabolic analysis of human tissues and biological fluids reveals the complex interactions among individual genetics, proteins, and environmental factors^[3]. We are optimistic about using metabolite analysis to monitor PD progression. Specifically, lipid metabolism-related products may serve as biomarkers for diagnosing PD. Current research indicates that α -synuclein is linked to FA uptake, cholesterol metabolism, and phospholipid activity. Recent population cohort studies have investigated lipid metabolism patterns in PD patients. For example, Choe *et al.* performed lipid profiling in 294 PD patients and 588 healthy

individuals, finding that PD patients had lower levels of high-density lipoprotein cholesterol but higher levels of lipoprotein A compared to controls^[148]. Additionally, Dahabiyeh *et al.* discovered that PD patients had higher serum levels of saturated lysophosphatidylcholine, unsaturated triglycerides, and hydroxyecosatetraenoic acid, while levels of neuroamide, sphingomyelin, and phosphatidylserine were lower^[149]. These findings suggest that lipid imbalances and dysfunctions in lipid pathways are significant biomarkers for PD diagnosis.

CONCLUSION

In conclusion, the accumulating evidence highlights the importance of dysregulated energy metabolism in glial cells in relation to aging and neurodegeneration. Nonetheless, substantial strides are necessary to devise novel therapeutic approaches for neurodegenerative ailments, including PD, through the manipulation of glial bioenergetics. Numerous pivotal inquiries remain unresolved and await comprehensive elucidation. Firstly, initial investigations on elderly individuals and patients primarily focus on observing correlations rather than establishing causation. Unraveling the metabolic alterations that either result from or lead to neuronal death poses a significant challenge. The substantial disparities between rodent models and human physiology limit the ability of animal studies to comprehensively address this issue. Innovative imaging techniques that integrate PET, computed tomography (CT), and magnetic resonance imaging (MRI) show promise in potentially unlocking insights into this complex problem. Secondly, the intricate molecular mechanisms governing the transition between different metabolic patterns in glial cells remain largely elusive. While the HIF-1 α is a recognized key regulator, it fails to account for all observations, particularly the shift from glycolysis to mitochondrial oxidative phosphorylation in reactive astrocytes. Unraveling the regulatory network that underlies energy metabolic reprogramming is crucial for identifying novel druggable targets. Last but not least, the investigation into the interplay among diverse metabolic pathways in disease-associated glial cells is imperative, given that many patients with neurodegenerative disorders also present with metabolic dysregulations like hyperlipidemia and hyperglycemia. Ideally, a comprehensive patient management approach for neurodegenerative diseases should be devised to address metabolic disorders while safeguarding vulnerable neurons.

DECLARATIONS

Authors' contributions

Literature search, writing, and original draft preparation: Chu B, Xiang H, Wang H, Lin Y, Li R
Conceptualization, review, revision, and editing: Qian H, Hu J

Availability of data and materials

Not applicable.

Financial support and sponsorship

This study was supported by the National Natural Science Foundation of China (82271276 to Qian H; 12102086 to Hu J) and Sichuan Provincial Science and Technology Department (Sichuan Provincial Science and Technology Project, Key R&D Program, 2022YFS0599 to Qian H).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2024.

REFERENCES

1. Vaupel JW. Biodemography of human ageing. *Nature* 2010;464:536-42. DOI PubMed PMC
2. Mattson MP, Arumugam TV. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. *Cell Metab* 2018;27:1176-99. DOI PubMed PMC
3. Emamzadeh FN, Surguchov A. Parkinson's disease: biomarkers, treatment, and risk factors. *Front Neurosci* 2018;12:612. DOI PubMed PMC
4. Magistretti PJ, Pellerin L, Rothman DL, Shulman RG. Energy on demand. *Science* 1999;283:496-7. DOI PubMed
5. Zheng X, Boyer L, Jin M, et al. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. *Elife* 2016;5:e13374. DOI PubMed PMC
6. Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. *Cell Metab* 2011;14:724-38. DOI PubMed
7. Sá JV, Kleiderman S, Brito C, et al. Quantification of metabolic rearrangements during neural stem cells differentiation into astrocytes by metabolic flux analysis. *Neurochem Res* 2017;42:244-53. DOI PubMed
8. Weightman Potter PG, Vlachaki Walker JM, Robb JL, et al. Basal fatty acid oxidation increases after recurrent low glucose in human primary astrocytes. *Diabetologia* 2019;62:187-98. DOI PubMed PMC
9. Mann K, Deny S, Ganguli S, Clandinin TR. Coupling of activity, metabolism and behaviour across the *Drosophila* brain. *Nature* 2021;593:244-8. DOI PubMed PMC
10. Beard E, Lengacher S, Dias S, Magistretti PJ, Finsterwald C. Astrocytes as key regulators of brain energy metabolism: new therapeutic perspectives. *Front Physiol* 2021;12:825816. DOI PubMed PMC
11. Yakushev I, Schreckenberger M, Müller MJ, et al. Functional implications of hippocampal degeneration in early Alzheimer's disease: a combined DTI and PET study. *Eur J Nucl Med Mol Imaging* 2011;38:2219-27. DOI PubMed
12. Bateman RJ, Xiong C, Benzinger TLS, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 2012;367:795-804. DOI PubMed PMC
13. Matthews DC, Lerman H, Lukic A, et al. FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. *Neuroimage Clin* 2018;20:572-9. DOI PubMed PMC
14. Ciarmiello A, Cannella M, Lastoria S, et al. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *J Nucl Med* 2006;47:215-22. PubMed
15. Cistaro A, Valentini MC, Chiò A, et al. Brain hypermetabolism in amyotrophic lateral sclerosis: a FDG PET study in ALS of spinal and bulbar onset. *Eur J Nucl Med Mol Imaging* 2012;39:251-9. DOI PubMed
16. Diehl-Schmid J, Licata A, Goldhardt O, et al; FTLDC Study Group. FDG-PET underscores the key role of the thalamus in frontotemporal lobar degeneration caused by C9ORF72 mutations. *Transl Psychiatry* 2019;9:54. DOI PubMed PMC
17. Ionescu-Tucker A, Cotman CW. Emerging roles of oxidative stress in brain aging and Alzheimer's disease. *Neurobiol Aging* 2021;107:86-95. DOI PubMed
18. Kishida KT, Klann E. Sources and targets of reactive oxygen species in synaptic plasticity and memory. *Antioxid Redox Signal* 2007;9:233-44. DOI PubMed PMC
19. Trist BG, Hare DJ, Double KL. Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. *Aging Cell* 2019;18:e13031. DOI PubMed PMC
20. Pandya JD, Grondin R, Yonutas HM, et al. Decreased mitochondrial bioenergetics and calcium buffering capacity in the basal ganglia correlates with motor deficits in a nonhuman primate model of aging. *Neurobiol Aging* 2015;36:1903-13. DOI PubMed
21. Alqahtani T, Deore SL, Kide AA, et al. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease, and Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis - an updated review. *Mitochondrion* 2023;71:83-92. DOI PubMed
22. Murray TE, Richards CM, Robert-Gostlin VN, Bernath AK, Lindhout IA, Klegeris A. Potential neurotoxic activity of diverse molecules released by astrocytes. *Brain Res Bull* 2022;189:80-101. DOI PubMed
23. Vicente-Gutierrez C, Bonora N, Bobo-Jimenez V, et al. Astrocytic mitochondrial ROS modulate brain metabolism and mouse behaviour. *Nat Metab* 2019;1:201-11. DOI PubMed
24. Miao J, Chen L, Pan X, Li L, Zhao B, Lan J. Microglial metabolic reprogramming: emerging insights and therapeutic strategies in neurodegenerative diseases. *Cell Mol Neurobiol* 2023;43:3191-210. DOI PubMed
25. Traxler L, Lagerwall J, Eichhorner S, Stefanoni D, D'Alessandro A, Mertens J. Metabolism navigates neural cell fate in development, aging and neurodegeneration. *Dis Model Mech* 2021;14:dmm048993. DOI PubMed PMC
26. Chamberlain KA, Sheng ZH. Mechanisms for the maintenance and regulation of axonal energy supply. *J Neurosci Res* 2019;97:897-913. DOI PubMed PMC

27. Shan L, Zhang T, Fan K, Cai W, Liu H. Astrocyte-neuron signaling in synaptogenesis. *Front Cell Dev Biol* 2021;9:680301. DOI PubMed PMC
28. Yang K, Wu Z, Long J, et al. White matter changes in Parkinson's disease. *NPJ Parkinsons Dis* 2023;9:150. DOI PubMed PMC
29. Depp C, Sun T, Sasmita AO, et al. Myelin dysfunction drives amyloid- β deposition in models of Alzheimer's disease. *Nature* 2023;618:349-57. DOI PubMed PMC
30. Takahashi S. Metabolic contribution and cerebral blood flow regulation by astrocytes in the neurovascular unit. *Cells* 2022;11:813. DOI PubMed PMC
31. Nippert AR, Chiang PP, Del Franco AP, Newman EA. Astrocyte regulation of cerebral blood flow during hypoglycemia. *J Cereb Blood Flow Metab* 2022;42:1534-46. DOI PubMed PMC
32. Chen Z, Yuan Z, Yang S, et al. Brain energy metabolism: astrocytes in neurodegenerative diseases. *CNS Neurosci Ther* 2023;29:24-36. DOI PubMed PMC
33. Briski KP, Ibrahim MMH, Mahmood ASMH, Alshamrani AA. Norepinephrine regulation of ventromedial hypothalamic nucleus astrocyte glycogen metabolism. *Int J Mol Sci* 2021;22:759. DOI PubMed PMC
34. Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proc Natl Acad Sci U S A* 1994;91:10625-9. DOI PubMed PMC
35. Benarroch EE. Neuron-astrocyte interactions: partnership for normal function and disease in the central nervous system. *Mayo Clin Proc* 2005;80:1326-38. DOI PubMed
36. Cortes-Campos C, Elizondo R, Carril C, et al. MCT2 expression and lactate influx in anorexigenic and orexigenic neurons of the arcuate nucleus. *PLoS One* 2013;8:e62532. DOI PubMed PMC
37. Roumes H, Jollé C, Blanc J, et al. Lactate transporters in the rat barrel cortex sustain whisker-dependent BOLD fMRI signal and behavioral performance. *Proc Natl Acad Sci U S A* 2021;118:e2112466118. DOI PubMed PMC
38. Muraleedharan R, Gawali MV, Tiwari D, et al. AMPK-regulated astrocytic lactate shuttle plays a non-cell-autonomous role in neuronal survival. *Cell Rep* 2020;32:108092. DOI PubMed PMC
39. Boisvert MM, Erikson GA, Shokhirev MN, Allen NJ. The aging astrocyte transcriptome from multiple regions of the mouse brain. *Cell Rep* 2018;22:269-85. DOI PubMed PMC
40. Ebert D, Haller RG, Walton ME. Energy contribution of octanoate to intact rat brain metabolism measured by ^{13}C nuclear magnetic resonance spectroscopy. *J Neurosci* 2003;23:5928-35. DOI PubMed PMC
41. Cashikar AG, Toral-Rios D, Timm D, et al. Regulation of astrocyte lipid metabolism and ApoE secretion by the microglial oxysterol, 25-hydroxycholesterol. *J Lipid Res* 2023;64:100350. DOI PubMed PMC
42. van Deijk AF, Camargo N, Timmerman J, et al. Astrocyte lipid metabolism is critical for synapse development and function in vivo. *Glia* 2017;65:670-82. DOI PubMed
43. Ioannou MS, Jackson J, Sheu SH, et al. Neuron-astrocyte metabolic coupling protects against activity-induced fatty acid toxicity. *Cell* 2019;177:1522-35.e14. DOI PubMed
44. Wright-Jin EC, Gutmann DH. Microglia as dynamic cellular mediators of brain function. *Trends Mol Med* 2019;25:967-79. DOI PubMed PMC
45. Bernier LP, York EM, Kamyabi A, Choi HB, Weilinger NL, MacVicar BA. Microglial metabolic flexibility supports immune surveillance of the brain parenchyma. *Nat Commun* 2020;11:1559. DOI PubMed PMC
46. Nagy AM, Fekete R, Horvath G, et al. Versatility of microglial bioenergetic machinery under starving conditions. *Biochim Biophys Acta Bioenerg* 2018;1859:201-14. DOI PubMed
47. Sabogal-Guáqueta AM, Marmolejo-Garza A, Trombetta-Lima M, et al. Species-specific metabolic reprogramming in human and mouse microglia during inflammatory pathway induction. *Nat Commun* 2023;14:6454. DOI PubMed PMC
48. Diemel GA. Brain glucose metabolism: integration of energetics with function. *Physiol Rev* 2019;99:949-1045. DOI PubMed
49. Tawbeh A, Gondcaille C, Tromprier D, Savary S. Peroxisomal ABC transporters: an update. *Int J Mol Sci* 2021;22:6093. DOI PubMed PMC
50. Huang SC, Smith AM, Everts B, et al. Metabolic reprogramming mediated by the mTORC2-IRF4 signaling axis is essential for macrophage alternative activation. *Immunity* 2016;45:817-30. DOI PubMed PMC
51. Van den Bossche J, O'Neill LA, Menon D. Macrophage immunometabolism: where are we (going)? *Trends Immunol* 2017;38:395-406. DOI PubMed
52. Vats D, Mukundan L, Odegaard JI, et al. Oxidative metabolism and PGC-1 β attenuate macrophage-mediated inflammation. *Cell Metab* 2006;4:13-24. DOI PubMed PMC
53. Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* 2011;333:1456-8. DOI PubMed
54. Drummond RA, Swamydas M, Oikonomou V, et al. CARD9 $^{+}$ microglia promote antifungal immunity via IL-1 β - and CXCL1-mediated neutrophil recruitment. *Nat Immunol* 2019;20:559-70. DOI PubMed PMC
55. Huang X, Guo M, Zhang Y, et al. Microglial IL-1RA ameliorates brain injury after ischemic stroke by inhibiting astrocytic CXCL1-mediated neutrophil recruitment and microvessel occlusion. *Glia* 2023;71:1607-25. DOI PubMed
56. Hsieh CF, Liu CK, Lee CT, Yu LE, Wang JY. Acute glucose fluctuation impacts microglial activity, leading to inflammatory activation or self-degradation. *Sci Rep* 2019;9:840. DOI PubMed PMC
57. Paolicelli RC, Sierra A, Stevens B, et al. Microglia states and nomenclature: a field at its crossroads. *Neuron* 2022;110:3458-83. DOI

[PubMed PMC](#)

58. Tagliatti E, Desiato G, Mancinelli S, et al. Trem2 expression in microglia is required to maintain normal neuronal bioenergetics during development. *Immunity* 2024;57:86-105.e9. [DOI PubMed PMC](#)
59. Cserép C, Pósfai B, Lénárt N, et al. Microglia monitor and protect neuronal function through specialized somatic purinergic junctions. *Science* 2020;367:528-37. [DOI PubMed](#)
60. Joshi AU, Mochly-Rosen D. Mortal engines: mitochondrial bioenergetics and dysfunction in neurodegenerative diseases. *Pharmacol Res* 2018;138:2-15. [DOI PubMed PMC](#)
61. García-Cáceres C, Bolland E, Prevot V, et al. Role of astrocytes, microglia, and tanycytes in brain control of systemic metabolism. *Nat Neurosci* 2019;22:7-14. [DOI PubMed](#)
62. Henn RE, Guo K, Elzinga SE, et al. Single-cell RNA sequencing identifies hippocampal microglial dysregulation in diet-induced obesity. *iScience* 2023;26:106164. [DOI PubMed PMC](#)
63. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci* 2003;23:3295-301. [DOI PubMed PMC](#)
64. Driscoll I, Davatzikos C, An Y, et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology* 2009;72:1906-13. [DOI PubMed PMC](#)
65. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB; Alzheimer's Disease Neuroimaging Initiative. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Prog Neurobiol* 2014;117:20-40. [DOI PubMed PMC](#)
66. Manard M, Bahri MA, Salmon E, Collette F. Relationship between grey matter integrity and executive abilities in aging. *Brain Res* 2016;1642:562-80. [DOI PubMed](#)
67. Liu H, Wang L, Geng Z, et al. A voxel-based morphometric study of age- and sex-related changes in white matter volume in the normal aging brain. *Neuropsychiatr Dis Treat* 2016;12:453-65. [DOI PubMed PMC](#)
68. Kwak K, Giovanello KS, Bozoki A, Styner M, Dayan E; Alzheimer's Disease Neuroimaging Initiative. Subtyping of mild cognitive impairment using a deep learning model based on brain atrophy patterns. *Cell Rep Med* 2021;2:100467. [DOI PubMed PMC](#)
69. Diel GA, Rothman DL. Reevaluation of astrocyte-neuron energy metabolism with astrocyte volume fraction correction: impact on cellular glucose oxidation rates, glutamate-glutamine cycle energetics, glycogen levels and utilization rates vs. exercising muscle, and Na⁺/K⁺ pumping rates. *Neurochem Res* 2020;45:2607-30. [DOI PubMed](#)
70. Boley N, Patil S, Garnett EO, et al. Association between gray matter volume variations and energy utilization in the brain: implications for developmental stuttering. *J Speech Lang Hear Res* 2021;64:2317-24. [DOI PubMed PMC](#)
71. Raiko JRH, Tuulari JJ, Saari T, et al. Associations between brain gray matter volumes and adipose tissue metabolism in healthy adults. *Obesity* 2021;29:543-9. [DOI PubMed](#)
72. Thambisetty M, Beason-Held LL, An Y, et al. Impaired glucose tolerance in midlife and longitudinal changes in brain function during aging. *Neurobiol Aging* 2013;34:2271-6. [DOI PubMed PMC](#)
73. Vagnoni A, Hoffmann PC, Bullock SL. Reducing Lissencephaly-1 levels augments mitochondrial transport and has a protective effect in adult *Drosophila* neurons. *J Cell Sci* 2016;129:178-90. [DOI PubMed PMC](#)
74. Yarchoan M, Toledo JB, Lee EB, et al. Abnormal serine phosphorylation of insulin receptor substrate 1 is associated with tau pathology in Alzheimer's disease and tauopathies. *Acta Neuropathol* 2014;128:679-89. [DOI PubMed PMC](#)
75. Mattson MP. Roles of the lipid peroxidation product 4-hydroxynonenal in obesity, the metabolic syndrome, and associated vascular and neurodegenerative disorders. *Exp Gerontol* 2009;44:625-33. [DOI PubMed PMC](#)
76. Delgado T, Petralia RS, Freeman DW, et al. Comparing 3D ultrastructure of presynaptic and postsynaptic mitochondria. *Biol Open* 2019;8:bio044834. [DOI PubMed PMC](#)
77. Faït J, Lacefield C, Davey T, et al. 3D neuronal mitochondrial morphology in axons, dendrites, and somata of the aging mouse hippocampus. *Cell Rep* 2021;36:109509. [DOI PubMed PMC](#)
78. Salvadores N, Sanhueza M, Manque P, Court FA. Axonal degeneration during aging and its functional role in neurodegenerative disorders. *Front Neurosci* 2017;11:451. [DOI PubMed PMC](#)
79. Stahon KE, Bastian C, Griffith S, Kidd GJ, Brunet S, Baltan S. Age-related changes in axonal and mitochondrial ultrastructure and function in white matter. *J Neurosci* 2016;36:9990-10001. [DOI PubMed PMC](#)
80. Stargardt A, Swaab DF, Bossers K. Storm before the quiet: neuronal hyperactivity and A β in the presymptomatic stages of Alzheimer's disease. *Neurobiol Aging* 2015;36:1-11. [DOI PubMed](#)
81. Lockwood CT, Duffy CJ. Hyperexcitability in aging is lost in Alzheimer's: what is all the excitement about? *Cereb Cortex* 2020;30:5874-84. [DOI PubMed PMC](#)
82. Goyal MS, Vlassenko AG, Blazey TM, et al. Loss of brain aerobic glycolysis in normal human aging. *Cell Metab* 2017;26:353-60.e3. [DOI PubMed PMC](#)
83. Cotto B, Natarajaseenivasan K, Langford D. Astrocyte activation and altered metabolism in normal aging, age-related CNS diseases, and HAND. *J Neurovirol* 2019;25:722-33. [DOI PubMed PMC](#)
84. Boumezbaur F, Mason GF, de Graaf RA, et al. Altered brain mitochondrial metabolism in healthy aging as assessed by *in vivo* magnetic resonance spectroscopy. *J Cereb Blood Flow Metab* 2010;30:211-21. [DOI PubMed PMC](#)
85. Clarke LE, Liddel SA, Chakraborty C, Münch AE, Heiman M, Barres BA. Normal aging induces A1-like astrocyte reactivity. *Proc Natl Acad Sci U S A* 2018;115:E1896-905. [DOI PubMed PMC](#)

86. Jiang T, Cadenas E. Astrocytic metabolic and inflammatory changes as a function of age. *Aging Cell* 2014;13:1059-67. DOI PubMed PMC
87. McNair LM, Andersen JV, Waagepetersen HS. Stable isotope tracing reveals disturbed cellular energy and glutamate metabolism in hippocampal slices of aged male mice. *Neurochem Int* 2023;171:105626. DOI PubMed
88. de Ceglia R, Ledonne A, Litvin DG, et al. Specialized astrocytes mediate glutamatergic gliotransmission in the CNS. *Nature* 2023;622:120-9. DOI PubMed PMC
89. Mela V, Mota BC, Milner M, et al. Exercise-induced re-programming of age-related metabolic changes in microglia is accompanied by a reduction in senescent cells. *Brain Behav Immun* 2020;87:413-28. DOI PubMed
90. Minhas PS, Latif-Hernandez A, McReynolds MR, et al. Restoring metabolism of myeloid cells reverses cognitive decline in ageing. *Nature* 2021;590:122-8. DOI PubMed PMC
91. Hickman SE, Kingery ND, Ohsumi TK, et al. The microglial sensome revealed by direct RNA sequencing. *Nat Neurosci* 2013;16:1896-905. DOI PubMed PMC
92. Lee S, Devanney NA, Golden LR, et al. APOE modulates microglial immunometabolism in response to age, amyloid pathology, and inflammatory challenge. *Cell Rep* 2023;42:112196. DOI PubMed PMC
93. Victor MB, Leary N, Luna X, et al. Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. *Cell Stem Cell* 2022;29:1197-212.e8. DOI PubMed PMC
94. Marschallinger J, Iram T, Zardeneta M, et al. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nat Neurosci* 2020;23:194-208. DOI PubMed PMC
95. Yen JJ, Yu II. The role of ApoE-mediated microglial lipid metabolism in brain aging and disease. *Immunometabolism* 2023;5:e00018. DOI PubMed PMC
96. Ross GW, Petrovitch H, Abbott RD, et al. Parkinsonian signs and substantia nigra neuron density in decedents elders without PD. *Ann Neurol* 2004;56:532-9. DOI PubMed
97. Vanitallie TB. Parkinson disease: primacy of age as a risk factor for mitochondrial dysfunction. *Metabolism* 2008;57 Suppl 2:S50-5. DOI PubMed
98. Rudow G, O'Brien R, Savonenko AV, et al. Morphometry of the human substantia nigra in ageing and Parkinson's disease. *Acta Neuropathol* 2008;115:461-70. DOI PubMed PMC
99. Elstner M, Morris CM, Heim K, et al. Expression analysis of dopaminergic neurons in Parkinson's disease and aging links transcriptional dysregulation of energy metabolism to cell death. *Acta Neuropathol* 2011;122:75-86. DOI PubMed
100. Keeney PM, Xie J, Capaldi RA, Bennett JP Jr. Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. *J Neurosci* 2006;26:5256-64. DOI PubMed PMC
101. Sherer TB, Betarbet R, Testa CM, et al. Mechanism of toxicity in rotenone models of Parkinson's disease. *J Neurosci* 2003;23:10756-64. DOI PubMed PMC
102. Requejo-Aguilar R, Lopez-Fabuel I, Fernandez E, Martins LM, Almeida A, Bolaños JP. PINK1 deficiency sustains cell proliferation by reprogramming glucose metabolism through HIF1. *Nat Commun* 2014;5:4514. DOI PubMed
103. Pissadaki EK, Bolam JP. The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson's disease. *Front Comput Neurosci* 2013;7:13. DOI PubMed PMC
104. Guzman JN, Sanchez-Padilla J, Wokosin D, et al. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. *Nature* 2010;468:696-700. DOI PubMed PMC
105. Xie B, Lin F, Ullah K, et al. A newly discovered neurotoxin ADTIQ associated with hyperglycemia and Parkinson's disease. *Biochem Biophys Res Commun* 2015;459:361-6. DOI PubMed
106. Chinta SJ, Andersen JK. Redox imbalance in Parkinson's disease. *Biochim Biophys Acta* 2008;1780:1362-7. DOI PubMed PMC
107. Huang M, Lou D, Charli A, et al. Mitochondrial dysfunction-induced H3K27 hyperacetylation perturbs enhancers in Parkinson's disease. *JCI Insight* 2021;6:e138088. DOI PubMed PMC
108. Fanning S, Haque A, Imberdis T, et al. Lipidomic analysis of α -synuclein neurotoxicity identifies stearoyl CoA desaturase as a target for parkinson treatment. *Mol Cell* 2019;73:1001-14.e8. DOI PubMed PMC
109. Zhao C, Tu J, Wang C, et al. Lysophosphatidylcholine binds α -synuclein and prevents its pathological aggregation. *Natl Sci Rev* 2024;11:nwae182. DOI PubMed PMC
110. Mazzio E, Soliman KF. The role of glycolysis and gluconeogenesis in the cytoprotection of neuroblastoma cells against 1-methyl 4-phenylpyridinium ion toxicity. *Neurotoxicology* 2003;24:137-47. DOI PubMed
111. Fernandes HJR, Patikas N, Foskolou S, et al. Single-cell transcriptomics of Parkinson's disease human in vitro models reveals dopamine neuron-specific stress responses. *Cell Rep* 2020;33:108263. DOI PubMed
112. Powers R, Lei S, Anandhan A, et al. Metabolic investigations of the molecular mechanisms associated with Parkinson's disease. *Metabolites* 2017;7:22. DOI PubMed PMC
113. Giordano S, Lee J, Darley-USmar VM, Zhang J. Distinct effects of rotenone, 1-methyl-4-phenylpyridinium and 6-hydroxydopamine on cellular bioenergetics and cell death. *PLoS One* 2012;7:e44610. DOI PubMed PMC
114. Lei S, Zavala-Flores L, Garcia-Garcia A, et al. Alterations in energy/redox metabolism induced by mitochondrial and environmental toxins: a specific role for glucose-6-phosphate-dehydrogenase and the pentose phosphate pathway in paraquat toxicity. *ACS Chem Biol* 2014;9:2032-48. DOI PubMed PMC
115. Butler EK, Voigt A, Lutz AK, et al. The mitochondrial chaperone protein TRAP1 mitigates α -synuclein toxicity. *PLoS Genet*

- 2012;8:e1002488. DOI PubMed PMC
116. Rothman SM, Griffioen KJ, Fishbein KW, et al. Metabolic abnormalities and hypoleptinemia in α -synuclein A53T mutant mice. *Neurobiol Aging* 2014;35:1153-61. DOI PubMed PMC
117. Müftüoğlu M, Elibol B, Dalmizrak O, et al. Mitochondrial complex I and IV activities in leukocytes from patients with parkin mutations. *Mov Disord* 2004;19:544-8. DOI PubMed
118. Wang HL, Chou AH, Wu AS, et al. PARK6 PINK1 mutants are defective in maintaining mitochondrial membrane potential and inhibiting ROS formation of substantia nigra dopaminergic neurons. *Biochim Biophys Acta* 2011;1812:674-84. DOI PubMed
119. Niu J, Yu M, Wang C, Xu Z. Leucine-rich repeat kinase 2 disturbs mitochondrial dynamics via dynamin-like protein. *J Neurochem* 2012;122:650-8. DOI PubMed
120. Requejo-Aguilar R, Lopez-Fabuel I, Jimenez-Blasco D, Fernandez E, Almeida A, Bolaños JP. DJ1 represses glycolysis and cell proliferation by transcriptionally up-regulating Pink1. *Biochem J* 2015;467:303-10. DOI PubMed PMC
121. Larsen NJ, Ambrosi G, Mullett SJ, Berman SB, Hinkle DA. DJ-1 knock-down impairs astrocyte mitochondrial function. *Neuroscience* 2011;196:251-64. DOI PubMed PMC
122. Kim JM, Cha SH, Choi YR, Jou I, Joe EH, Park SM. DJ-1 deficiency impairs glutamate uptake into astrocytes via the regulation of flotillin-1 and caveolin-1 expression. *Sci Rep* 2016;6:28823. DOI PubMed PMC
123. Cole NB, Murphy DD, Grider T, Rueter S, Brasaemle D, Nussbaum RL. Lipid droplet binding and oligomerization properties of the Parkinson's disease protein alpha-synuclein. *J Biol Chem* 2002;277:6344-52. DOI PubMed
124. Kim S, Pajarillo E, Nyarko-Danquah I, Aschner M, Lee E. Role of astrocytes in Parkinson's disease associated with genetic mutations and neurotoxins. *Cells* 2023;12:622. DOI PubMed PMC
125. Choi I, Kim J, Jeong HK, et al. PINK1 deficiency attenuates astrocyte proliferation through mitochondrial dysfunction, reduced AKT and increased p38 MAPK activation, and downregulation of EGFR. *Glia* 2013;61:800-12. DOI PubMed PMC
126. Cha SH, Choi YR, Heo CH, et al. Loss of parkin promotes lipid rafts-dependent endocytosis through accumulating caveolin-1: implications for Parkinson's disease. *Mol Neurodegener* 2015;10:63. DOI PubMed PMC
127. Sonninen TM, Hämäläinen RH, Koskivi M, et al. Metabolic alterations in Parkinson's disease astrocytes. *Sci Rep* 2020;10:14474. DOI PubMed PMC
128. Castagnet PI, Golovko MY, Barceló-Coblijn GC, Nussbaum RL, Murphy EJ. Fatty acid incorporation is decreased in astrocytes cultured from alpha-synuclein gene-ablated mice. *J Neurochem* 2005;94:839-49. DOI PubMed
129. Alecu I, Bennett SAL. Dysregulated lipid metabolism and its role in α -synucleinopathy in Parkinson's disease. *Front Neurosci* 2019;13:328. DOI PubMed PMC
130. Russ K, Teku G, Bousset L, et al. TNF- α and α -synuclein fibrils differently regulate human astrocyte immune reactivity and impair mitochondrial respiration. *Cell Rep* 2021;34:108895. DOI PubMed
131. Halliday GM, Stevens CH. Glia: initiators and progressors of pathology in Parkinson's disease. *Mov Disord* 2011;26:6-17. DOI PubMed
132. Peng Y, He J, Xiang H, et al. Potential impact of hypoxic astrocytes on the aggravation of depressive symptoms in Parkinson's disease. *J Mol Neurosci* 2024;74:28. DOI PubMed
133. Libro R, Bramanti P, Mazzon E. The role of the Wnt canonical signaling in neurodegenerative diseases. *Life Sci* 2016;158:78-88. DOI PubMed
134. Vallée A, Lecarpentier Y, Vallée JN. Circadian rhythms and energy metabolism reprogramming in Parkinson's disease. *Curr Issues Mol Biol* 2019;31:21-44. DOI PubMed
135. L'episcopo F, Serapide MF, Tirolo C, et al. A *Wnt1* regulated *Frizzled-1*/ β -*Catenin* signaling pathway as a candidate regulatory circuit controlling mesencephalic dopaminergic neuron-astrocyte crosstalk: Therapeutic relevance for neuron survival and neuroprotection. *Mol Neurodegener* 2011;6:49. DOI PubMed PMC
136. Yang S, Qin C, Hu ZW, et al. Microglia reprogram metabolic profiles for phenotype and function changes in central nervous system. *Neurobiol Dis* 2021;152:105290. DOI PubMed
137. Pajares M, I Rojo A, Manda G, Boscá L, Cuadrado A. Inflammation in Parkinson's disease: mechanisms and therapeutic implications. *Cells* 2020;9:1687. DOI PubMed PMC
138. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. *Annu Rev Immunol* 2017;35:441-68. DOI PubMed PMC
139. Lavis S, Goutal S, Wimberley C, et al. Increased microglial activation in patients with Parkinson disease using [18 F]-DPA714 TSPO PET imaging. *Parkinsonism Relat Disord* 2021;82:29-36. DOI PubMed
140. Gu R, Zhang F, Chen G, et al. Clk1 deficiency promotes neuroinflammation and subsequent dopaminergic cell death through regulation of microglial metabolic reprogramming. *Brain Behav Immun* 2017;60:206-19. DOI PubMed
141. Tu D, Gao Y, Yang R, Guan T, Hong JS, Gao HM. The pentose phosphate pathway regulates chronic neuroinflammation and dopaminergic neurodegeneration. *J Neuroinflammation* 2019;16:255. DOI PubMed PMC
142. Qiao H, He X, Zhang Q, et al. Alpha-synuclein induces microglial migration via PKM2-dependent glycolysis. *Int J Biol Macromol* 2019;129:601-7. DOI PubMed
143. Cheng SC, Quintin J, Cramer RA, et al. mTOR- and HIF-1 α -mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* 2014;345:1250684. DOI PubMed PMC
144. Baik SH, Kang S, Lee W, et al. A breakdown in metabolic reprogramming causes microglia dysfunction in Alzheimer's disease. *Cell*

- Metab* 2019;30:493-507.e6. [DOI](#) [PubMed](#)
145. Lu J, Wang C, Cheng X, et al. A breakdown in microglial metabolic reprogramming causes internalization dysfunction of α -synuclein in a mouse model of Parkinson's disease. *J Neuroinflammation* 2022;19:113. [DOI](#) [PubMed](#) [PMC](#)
 146. Szwed A, Kim E, Jacinto E. Regulation and metabolic functions of mTORC1 and mTORC2. *Physiol Rev* 2021;101:1371-426. [DOI](#) [PubMed](#) [PMC](#)
 147. Brekk OR, Honey JR, Lee S, Hallett PJ, Isacson O. Cell type-specific lipid storage changes in Parkinson's disease patient brains are recapitulated by experimental glycolipid disturbance. *Proc Natl Acad Sci U S A* 2020;117:27646-54. [DOI](#) [PubMed](#) [PMC](#)
 148. Choe CU, Petersen E, Lezius S, et al. Association of lipid levels with motor and cognitive function and decline in advanced Parkinson's disease in the Mark-PD study. *Parkinsonism Relat Disord* 2021;85:5-10. [DOI](#) [PubMed](#)
 149. Dahabiyeh LA, Nimer RM, Rashed M, Wells JD, Fiehn O. Serum-based lipid panels for diagnosis of idiopathic Parkinson's disease. *Metabolites* 2023;13:990. [DOI](#) [PubMed](#) [PMC](#)