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Opinion

Neuronal glycolysis meets mitophagy to govern organismal wellbeing

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Neurons are exceptionally energy-demanding cells but have limited energy storage, relying on a constant supply of fuel and oxygen. Although glucose is the brain's main energy source, neurons reduce glycolysis under normal conditions. This surprising strategy helps to protect mitochondria by preserving nicotinamide-adenine dinucleotide (NAD^+), a vital cofactor consumed by glycolysis. NAD^+ is needed for sirtuin-driven mitophagy, a process that removes damaged mitochondria. By saving NAD^+, neurons can maintain healthy, energy-efficient mitochondria. These mitochondria then use alternative fuels such as lactate and ketone bodies from astrocytes. Here, we discuss the way in which this balance between reduced glycolysis and active mitophagy supports brain function and overall metabolic health, highlighting a sophisticated system that prioritizes mitochondrial quality for long-term cognitive performance and systemic homeostasis.

Highlights

New research shows that neurons avoid using glucose for energy, and instead use lactate and ketone bodies from astrocytes, saving glucose to fight stress and prevent cell death.

Cutting-edge tools such as targeted genetic models and live metabolite sensors have revealed how neurons and astrocytes work together, highlighting the importance of nicotinamide-adenine dinucleotide (NAD^+), sirtuins, and mitophagy in keeping brain and body metabolism healthy.

These discoveries shift our understanding of brain disease, showing that problems with neuron metabolism – not just neurotransmitters – may drive conditions such as Alzheimer's disease and diabetes, pushing us toward treatments that focus on brain energy balance.

Understanding the high cost of neurotransmission

The proper functioning of an organism relies on the formation of neuronal circuits and effective synaptic transmission – processes that demand substantial energy to restore ion gradients across the neuronal membrane. It is widely accepted that glucose, delivered through cerebral vasculature, is the brain's primary metabolic substrate [1]. However, whether neurons rely on direct glucose metabolism or prefer astrocyte-derived substrates – such as lactate and **ketone bodies** (see Glossary) – for their energy needs has been the focus of extensive research [2–4]. For decades, technical limitations hindered *in vivo* resolution of this question. Recent advances, including genetically modified mice with cell-type-specific control of key metabolic enzymes [5,6], and the development of genetically encoded sensors for real-time metabolite tracking at cellular resolution [7,8], have propelled the field forward. Unfortunately, despite these advances, therapeutic strategies for neurodegenerative and metabolic diseases have lagged behind. Here, we highlight emerging evidence positioning the suppression of neuronal **glycolysis** and the support of astrocyte-derived metabolism as central strategies for preserving mitochondrial function, cognitive integrity, and systemic metabolic balance. By examining the glycolysis–**mitophagy** axis and **neuron–glia metabolic coupling**, we argue for a paradigm shift toward brain-centered interventions that address the root metabolic disruptions driving today's most pressing neurological and metabolic disorders.

Neuronal hypo-glycolytic metabolism spares glucose for antiapoptotic purposes

Unlike astrocytes, neurons do not directly contact brain blood vessels [9], making their access to circulating glucose limited. Consequently, it is plausible to propose that neurons preserve glucose for functions beyond mere energy production, which demands a considerable supply for glycolysis. Indeed, evidence from cultured neurons indicates a preferential metabolism of glucose-6-phosphate (G6P) through the **pentose phosphate pathway** (**PPP**) (Figure 1) [10]. This pathway

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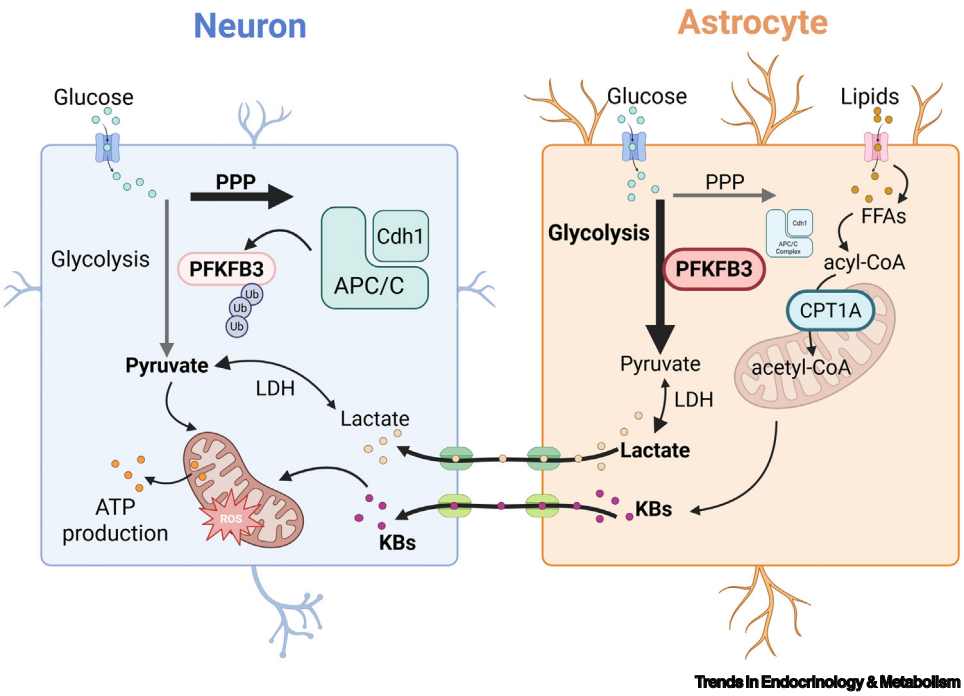

Figure 1. Metabolic interplay between astrocytes and neurons. Astrocytes preferentially engage in glycolysis, driven by high levels of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (Pfkfb3), and export lactate to neurons. Pyruvate derived from glycolysis in astrocytes is primarily converted to lactate, which is shuttled to neurons and taken up for oxidative metabolism. Neurons, in contrast, exhibit suppressed Pfkfb3 activity via APC/C-Cdh1-mediated ubiquitination, favoring the pentose phosphate pathway (PPP) and mitochondrial oxidative phosphorylation for ATP production. Neurons use lactate and ketone bodies (KBs) from astrocytes to generate energy while minimizing oxidative stress. Additionally, astrocytes utilize fatty acids (FFAs) via CPT1A-mediated β-oxidation, further supporting ketone body production and maintaining redox balance. This compartmentalized metabolic cooperation is crucial for neuronal function and survival under both physiological and pathological conditions. Abbreviation: LDH, lactate dehydrogenase. Figure created using BioRender.

generates NADPH(H^+), an essential cofactor for glutathione reductase, a key antioxidant enzyme [11]. Thus, neuronal glucose metabolism via the PPP appears to be a strategic adaptation to counteract redox stress and prevent apoptosis [10,12]. Interestingly, not only neurons but also cancer cells exploit a similar mechanism to evade apoptosis [12,13]. Since the PPP and glycolysis share G6P as a common precursor, they inherently compete for this metabolite. This metabolic tug-of-war has been demonstrated in primary neurons genetically modified to enhance glycolysis via overexpression of the pro-glycolytic enzyme **6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3** (**Pfkfb3**) (Box 1). These neurons exhibited suppressed PPP activity, elevated oxidative stress, and ultimately underwent apoptosis [10]. Such findings support the notion that neurons regard glucose as a vital resource, preferentially channeled towards redox homeostasis rather than ATP production. Instead, neurons may rely on alternative energy substrates, supplied through intercellular metabolic cooperation, to support neurotransmission.

Astrocyte-derived metabolic support sustains neuronal energy needs

Beyond their role in neurotransmitter recycling, astrocytes play a central metabolic role by supplying neurons with critical energy substrates and the precursors necessary for biosynthesis [14]. For instance, astrocytes exhibit higher glycolytic activity than neurons [15,16] (Box 1 and Figure 1). This metabolic engagement correlates with neuronal activity, as evidenced by *in vivo* positron emission tomography (PET) studies [17,18]. Notably, activation of glutamate receptors in astrocytes enhances glucose uptake and promotes lactate release [2], thereby establishing

Glossary

Glycolysis: the process of breaking down glucose into pyruvate, yielding ATP and NADH. While it is a major energy source in many cells, neurons suppress glycolysis to prioritize protective pathways like the PPP. Excessive glycolysis in neurons, often triggered by pathological cues, increases oxidative damage and disrupts cellular homeostasis. Thus, regulated glycolytic activity is essential for maintaining neuronal health.

Ketone bodies: energy-rich molecules – mainly acetoacetate and β-hydroxybutyrate – produced in astrocytes from fatty acid β-oxidation. During high energy demand or low glucose, ketones are delivered to neurons, converted to acetyl-CoA, and used in the TCA cycle for ATP. This astrocyte-to-neuron fuel sharing supports neuronal energy while conserving glucose, helping to maintain redox balance and reduce oxidative stress.

Mitophagy: selective removal of damaged or unnecessary mitochondria via autophagy. In neurons, mitophagy preserves mitochondrial quality, crucial for energy production, synaptic function, and longevity. Efficient mitophagy prevents ROS accumulation and cell death. It is regulated by NAD^+-dependent enzymes such as sirtuins, guarding against neurodegeneration and age-related decline.

Nicotinamide-adenine dinucleotide (NAD^+): a central coenzyme in redox reactions and a substrate for enzymes such as sirtuins and PARPs. In neurons, NAD^+ supports mitochondrial health, mitophagy, and stress responses. Its depletion impairs these defenses, leading to energy failure and degeneration. NAD^+ replenishment through precursors such as NMN is being explored for brain protection and longevity.

Neuron–glia metabolic coupling: the shared metabolic roles between astrocytes and neurons. Astrocytes convert glucose into lactate and ketones, which neurons use for energy via oxidative phosphorylation. This specialization allows neurons to conserve glucose for antioxidant defense and genome maintenance. It reduces glycolytic stress and protects neurons under high activity or metabolic pressure.

Box 1. Coordination of neuronal and astrocytic glycolysis by Pfkfb3

The rate of glucose breakdown through glycolysis is largely regulated by the enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (Pfkfb3) [10]. This enzyme produces fructose-2,6-bisphosphate, a powerful activator of 6-phosphofructo-1-kinase (Pfk1), which is a key control point in glycolysis [58,59]. In astrocytes, Pfkfb3 is stable and active, allowing these cells to maintain high glycolytic activity [10]. However, in neurons, Pfkfb3 is constantly broken down by the anaphase-promoting complex/cyclosome (APC/C), a type of E3 ubiquitin ligase. This process is driven by the cofactor CDH1 (cell division cycle 20 homolog 1), since the alternative cofactor CDC20 (cell division cycle 20) is not expressed in mature neurons [60,61]. As a result, neurons are unable to sustain high glycolytic rates under normal conditions, although temporary activation of glycolysis can occur in specific cellular compartments under certain stimuli [62]. One such case involves activation of glutamate receptors, which increases intracellular Ca^{2+} and triggers the cleavage of p35 into p25, a strong activator of cyclin-dependent kinase-5 (Cdk5). This leads to hyperphosphorylation of CDH1, detaching it from APC/C and inhibiting its activity [63]. Without APC/C, Pfkfb3 (and other substrates like cyclin B1 and Rock2) accumulates, turning on glycolysis in neurons – but at a cost. This delayed activation contributes to neuronal apoptosis [63–65]. In fact, inappropriate stabilization of neuronal Pfkfb3 has been observed in various disease states [57,66]. In Alzheimer's disease (AD), excessive glycolysis in neurons – referred to as neuronal hyperglycolysis – has emerged as a metabolic hallmark, contributing to increased neuronal death and overall dysfunction [67].

Pentose phosphate pathway (PPP): a metabolic route, branching from glycolysis, that generates NADPH and ribose-5-phosphate. Neurons rely on the PPP to produce NADPH, essential for antioxidant systems such as glutathione. Prioritizing the PPP over glycolysis enhances resilience to oxidative stress and helps to prevent apoptosis under challenging conditions.

6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (Pfkfb3): an enzyme that promotes glycolysis by increasing fructose-2,6-bisphosphate, a key activator of phosphofructokinase-1. Normally degraded in neurons to suppress glycolysis and favor the PPP, Pfkfb3 becomes harmful when stabilized. This leads to excess glycolysis, mitochondrial stress, and neuronal death – revealing the need for tightly controlled metabolic balance.

an astrocyte-to-neuron lactate gradient, as demonstrated *in vivo* [19]. In addition to lactate, emerging evidence indicates that astrocytes actively produce ketone bodies – specifically β-hydroxybutyrate and acetoacetate – from fatty acids derived either endogenously [5] or released by neurons [20]. This metabolic pathway begins with mitochondrial β-oxidation, which generates acetyl-CoA. In astrocytes, approximately two-thirds of the acetyl-CoA derived from β-oxidation is converted into ketone bodies (ketogenesis) and subsequently released into the extracellular space [5]. Neurons then take up both glycolysis-derived lactate and β-oxidation-derived ketone bodies produced by astrocytes, converting them into acetyl-CoA to fuel the tricarboxylic acid (TCA) cycle. This process enables mitochondrial ATP production [5,20–22], which is essential to support synaptic activity [23] (Figure 1). Therefore, compelling evidence supports a model in which neuronal mitochondria generate the energy required for brain function by utilizing metabolic substrates supplied by astrocytes, thereby sparing glucose for redox balance and anti-apoptotic mechanisms. Crucially, the sustainability of this model relies on the maintenance of exceptionally healthy and metabolically efficient mitochondria within neurons.

Glycolysis regulates NAD^+ pool homeostasis in neurons

A compelling approach to demonstrate *in vivo* the necessity of astrocyte–neuron metabolic cooperation for brain function involves genetically engineering mice to express an active glycolytic phenotype specifically in neurons. In a recent study, a mouse model was developed in which the glycolysis-promoting enzyme Pfkfb3 was selectively expressed in cerebral neurons [6] (Figure 2). These neurons exhibited increased glycolytic flux *in vivo*, but also showed multiple pathophysiological alterations, including accumulation of damaged mitochondria, impaired bioenergetics, and elevated redox stress [6]. Notably, these mice rapidly developed severe systemic consequences, such as cognitive impairment and a metabolic syndrome-like syndrome [6]. Glycolysis requires continuous regeneration of **NAD^+**, which is reduced to NADH(H^+) during the reaction catalyzed by glyceraldehyde-3-phosphate dehydrogenase. Under physiological conditions, NAD^+ is regenerated via three main mechanisms: lactate dehydrogenase (LDH), the malate/aspartate shuttle, and the glycerol-3-phosphate shuttle. However, neurons predominantly express an LDH isoform that converts lactate into pyruvate, a reaction that consumes rather than replenishes NAD^+ [24,25]. Accordingly, neurons require intact and functional mitochondria to effectively regenerate cytosolic NAD^+ through the proper operation of the shuttle systems. In Pfkfb3-expressing neurons, the accumulation of dysfunctional mitochondria disrupted the function of these shuttles, leading to a failure in NAD^+ regeneration [6]. As a result, sustained glycolytic activity in neurons led to rapid NAD^+ depletion, contributing to the observed neurological and metabolic phenotypes (Figure 2). Remarkably, both cognitive and metabolic impairments

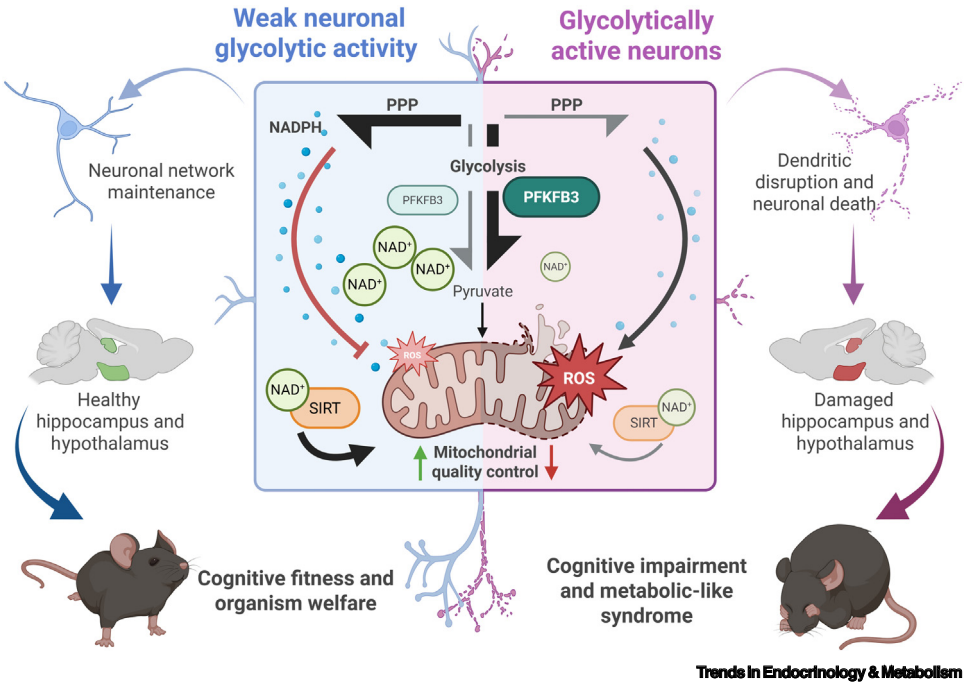

Figure 2. Neuronal glycolytic activity impacts brain homeostasis and systemic physiology. Neurons with attenuated glycolytic activity prioritize flux through the pentose phosphate pathway (PPP), promoting NADPH production and maintaining redox balance. This metabolic state supports neuronal and mitochondrial integrity via sirtuin-mediated mitophagy, contributing to healthy hippocampal and hypothalamic brain areas. Consequently, these processes sustain cognitive performance and overall organismal homeostasis (left). In contrast (right), glycolytically active neurons in genetically engineered mice expressing 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (Pfkfb3) exclusively in neurons, channel glucose metabolism predominantly through glycolysis, reducing NAD^+ levels and sirtuin-mediated mitophagy. This leads to an increase in damaged mitochondria that produce excess reactive oxygen species (ROS), propagating mitochondrial impairment, dendritic disruption, and promoting neuronal loss in the hippocampus and hypothalamus. These alterations culminate in cognitive deficits and features reminiscent of metabolic syndrome. Abbreviation: SIRT, sirtuin. Figure created using BioRender.

were reversed upon administration of nicotinamide mononucleotide (NMN), a NAD^+ precursor that restores its brain levels [6,26]. A similar finding was independently confirmed by a separate study [6,26], underscoring the critical importance of maintaining neuronal NAD^+ for cognitive function and metabolic health.

Glycolysis promotes mitophagy through sirtuin activation

To maintain mitochondrial integrity and meet energy demands, neurons rely on a balance between mitochondrial biogenesis and mitophagy [27]. Mitophagy removes damaged mitochondria by directing them to lysosomes for degradation and recycling [28]. When this process fails, defective mitochondria accumulate, disrupting metabolism, increasing oxidative stress, and triggering inflammation – key factors in aging and metabolic diseases [29–31]. Besides its role in glycolysis, NAD^+ is crucial for enzymes such as sirtuins and poly (ADP-ribose) polymerases (PARPs), which regulate stress responses, autophagy, and DNA repair [32–34]. Sirtuins have emerged as key regulators of metabolism [35,36]. These NAD^+-dependent deacetylases act as metabolic sensors, coordinating cellular responses to nutrient availability [37]. In particular, sirtuins regulate energy balance in the hypothalamus during caloric restriction [38], influencing feeding behavior, adiposity, and glucose tolerance [39]. NAD^+-independent mitophagy pathways are summarized in Box 2. Consistently, selective expression of Pfkfb3 in hypothalamic neurons is sufficient to

Box 2. NAD^+-independent mechanisms of mitochondrial quality control in neurons

PINK1/Parkin-dependent mitophagy

The PINK1/Parkin pathway is a well-characterized mechanism for mitochondrial quality control in neurons. When mitochondria become depolarized, PINK1 accumulates on their outer membrane, recruiting and activating the E3 ubiquitin ligase Parkin. Parkin ubiquitinates various mitochondrial surface proteins, marking the damaged mitochondria for degradation via autophagy. This pathway has been observed in human neurons and is crucial for maintaining mitochondrial integrity [68,69].

BNIP3 and NIX receptor-mediated mitophagy

BNIP3 and NIX (also known as BNIP3L) are mitophagy receptors located on the outer mitochondrial membrane. They can directly interact with LC3, a protein involved in autophagosome formation, facilitating the removal of damaged mitochondria. These receptors are particularly active under hypoxic conditions and during neuronal development. Elevated levels of BNIP3 and NIX have been associated with increased mitophagy in human neurons [70,71].

Mitochondrial dynamics: fission and fusion

Mitochondrial fission and fusion are dynamic processes that regulate mitochondrial morphology and function. Fission, mediated by proteins like Drp1, allows the segregation of damaged mitochondrial segments, which can then be targeted for mitophagy. Fusion helps maintain mitochondrial function by mixing the contents of partially damaged mitochondria. Disruptions in these processes can lead to impaired mitophagy and have been implicated in neurodegenerative diseases [72,73].

Transmitophagy: neuron-to-astrocyte mitochondrial transfer

Transmitophagy refers to the process in which neurons transfer damaged mitochondria to neighboring astrocytes for degradation. This intercellular mechanism has been observed in human induced pluripotent stem cell-derived astrocytes and is altered in conditions such as Alzheimer's disease [74,75].

induce a metabolic syndrome-like phenotype, including obesity [6,26]. This condition is marked by reduced NAD^+ levels, leading to impaired sirtuin-mediated mitophagy, elevated insulin and leptin, increased adiposity, and hyperphagia [6,26]. These findings underscore the tight link between glycolysis and mitophagy, where neurons must finely tune both pathways to avoid NAD^+ depletion (Figure 2). While glycolysis consumes NAD^+ for energy production, mitophagy depends on it to maintain mitochondrial turnover. At this metabolic crossroads, neurons bypass glycolysis to protect mitochondrial integrity – ensuring proper oxidation of glia-derived fuels.

Neuronal glycolysis regulates the neuroendocrine system

Despite major strides in understanding how the brain regulates energy balance and metabolism, progress in developing effective treatments for metabolic diseases has lagged behind [40,41]. One likely reason is our still-limited knowledge of the specific hypothalamic neurons and the complex neuroendocrine circuits that drive these processes [42]. At the center of this regulation is the arcuate nucleus, which acts like a metabolic sensor. It detects signals from hormones such as leptin, ghrelin, and insulin, as well as nutrients, through specialized receptors in two main neuronal populations: the orexigenic agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons and the anorexigenic pro-opiomelanocortin (POMC) neurons [43]. These neurons integrate signals and coordinate responses across brain regions to control hunger, satiety, energy use, glucose levels, and insulin sensitivity – essentially shaping whole-body metabolism through a diverse set of neural pathways [42]. Furthermore, obesity-induced chronic inflammation impairs key interfaces between the periphery and the brain – such as the blood–brain barrier (BBB) and the glymphatic system – disrupting hypothalamic signaling and increasing the risk of cognitive dysfunction [44]. In this context, new insights into neuroendocrine gut–brain communication have revealed how gastrointestinal signals dynamically shape feeding behavior and metabolic responses, underscoring the brain's role as a central integrator of peripheral metabolic cues [42,45]. Pfkfb3 plays a key role here. It acts as a nutrient sensor in these hypothalamic neurons, responding to feeding by promoting glycolysis, lowering AMP-activated protein kinase (AMPK)

phosphorylation, and changing neuropeptide expression in a way that suppresses appetite [46]. Lower AMPK activity activates acetyl-CoA carboxylase, raising malonyl-CoA levels, a molecule that tells the brain to curb food intake when glucose is plentiful [47,48]. Interestingly, fructose evades this control. Unlike glucose, it bypasses the glycolytic control step at Pfk1, so it is rapidly metabolized via glycolysis, leading to fast ATP consumption, which triggers a spike in AMP that activates AMPK and overrides the malonyl-CoA signal – essentially stimulating appetite instead of suppressing it [49]. This highlights how different nutrients can uniquely influence brain metabolism and feeding behavior, and why targeting these mechanisms may be key to future therapies.

Neuronal glycolysis governs mitophagy for cognition

Beyond their metabolic roles, sirtuins play a key part in cognitive functions such as learning and memory [50]. Emerging evidence underscores their importance in promoting synaptic plasticity and maintaining neuronal health by supporting mitochondrial biogenesis [51], clearing toxic aggregates such as polyglutamine and amyloid-β plaques [52], and boosting antioxidant defenses through FOXO protein activation [53]. These findings highlight the versatility of sirtuins and their growing potential as therapeutic targets for both metabolic and neurodegenerative diseases [54]. In line with this, excessive activation of neuronal glycolysis has been linked to dendritic damage and neuronal apoptosis across various brain regions, leading to cognitive deficits and impaired motor coordination [6,26]. Remarkably, replenishing brain NAD^+ levels through NMN supplementation was able to restore proper sirtuin-driven mitophagy and reverse these behavioral impairments [6]. This points to a direct link between glycolysis and mitophagy, with NAD^+ acting as a critical mediator. When glycolysis consumes too much NAD^+, mitophagy suffers – putting mitochondrial quality, and thus higher brain functions, at risk (Figure 2). Recent studies also suggest that enhancing selective autophagy pathways may offer promising therapeutic avenues against neurodegenerative diseases. For example, stimulating ER-phagy improved organismal fitness and reduced amyloid precursor protein toxicity in a *Drosophila* Alzheimer's model [55]. Likewise, boosting mitophagy in Alzheimer's models using *Caenorhabditis elegans* and mice reversed tau hyperphosphorylation and memory loss [29]. Taken together, these findings strongly argue that neurons must tightly regulate the balance between glycolytic activity and mitophagy to preserve mitochondrial function, and ultimately to safeguard cognitive performance and overall wellbeing.

Concluding remarks and future perspectives

Neurons adopt a unique metabolic strategy: they suppress glycolysis, not as a weakness, but as a protective adaptation to preserve mitochondrial integrity and support essential quality control processes such as mitophagy. This deliberate restraint ensures the maintenance of cellular redox balance and NAD^+ availability – key for activating sirtuins, which orchestrate mitochondrial function, stress responses, and neuronal longevity. Remarkably, despite downregulating a major ATP-generating pathway, neurons meet their high energy demands through a tight metabolic partnership with glial cells. This neuron–glia coupling supplies alternative substrates that are efficiently processed by neuronal mitochondria, emphasizing the indispensable role of glial support in sustaining neuronal energy homeostasis and function.

Yet, while our understanding of these fundamental mechanisms continues to deepen, the translation into effective therapies remains limited. Rates of obesity, type 2 diabetes, and neurodegenerative diseases continue to climb, and current interventions – though increasingly effective in symptom management – do not target the root disruptions in brain metabolic regulation. Recently approved anti-obesity drugs and immunotherapies aimed at cognitive symptoms in neurodegenerative diseases represent important progress. However, they largely act downstream of the primary neuronal and metabolic dysfunctions. In this context, emerging insights into the intersection

Outstanding questions

What molecular checkpoints regulate the balance between neuronal glycolysis and mitophagy under physiological and pathological conditions? Identifying these checkpoints may uncover mechanisms by which neurons suppress glycolysis to preserve NAD^+ and support mitochondrial quality control. A deeper understanding could inform interventions that restore this balance in disease states.

How do astrocyte-derived metabolic substrates influence neuronal NAD^+ dynamics and sirtuin activity across brain regions? Given the regional and functional diversity of astrocytes, exploring how their metabolic output shapes neuronal redox homeostasis and mitophagy may reveal region-specific vulnerabilities and therapeutic targets.

Can early-life metabolic interventions reprogram neuronal energy metabolism to prevent age-related cognitive decline and neurodegenerative disease? If metabolic programming in development influences lifelong neuronal health, identifying critical windows for intervention could lead to preventive strategies rather than reactive treatments.

How does chronic nutrient excess alter neuron-glia metabolic coupling, and can this disruption be reversed? Modern diets rich in glucose and fructose may overload glycolytic pathways and impair astrocyte-to-neuron substrate flow. Understanding whether and how this disruption can be restored is key to addressing metabolic syndrome and cognitive decline.

What are the long-term effects of modulating neuronal glycolysis or NAD^+ levels on systemic energy balance and behavior? Manipulating glycolytic activity or boosting NAD^+ shows promise in reversing metabolic and cognitive impairments, but the broader consequences on neuroendocrine circuits and whole-body homeostasis remain largely unknown.

of neuronal glycolysis and mitophagy open promising avenues. Evidence now points to the NAD^+–sirtuin axis as a central node in preserving neuronal health and systemic metabolic balance. Targeting neuronal-specific regulators such as Pfkfb3, maintaining NAD^+ levels in the brain, and leveraging sirtuin activation could form the basis for novel, mechanism-based strategies to address both metabolic and neurological pathologies. In the mouse, intracerebroventricular administration of selective Pfkfb3 inhibitors, at doses that minimize astrocytic Pfkfb3 activity while blocking neuronal Pfkfb3 [56], prevents neuronal death [57] and reduces infarct volume [56] in the neurodegenerative Batten's disease and middle cerebral artery occlusion models, respectively. These approaches promise not only to support neuronal survival and cognitive resilience but also to restore whole-body homeostasis.

The field is now poised to capitalize on transformative technologies – such as single-cell spatial metabolomics, wireless optogenetics, and high-resolution circuit tracing – that allow real-time dissection of discrete hypothalamic and extrahypothalamic networks. These tools will accelerate our understanding of how metabolic, hormonal, and environmental cues are integrated by the brain to regulate feeding, energy balance, and cognitive function. Looking ahead, several key questions remain (see Outstanding questions). How do chronic nutritional excess and redox imbalance disrupt these finely tuned neuronal circuits? Can early metabolic interventions recalibrate mitophagy and preserve neural function across the lifespan? And crucially, how might we design targeted, brain-centered therapies that go beyond symptom control to address the metabolic underpinnings of disease? Answering these questions will require a paradigm shift – one that places brain metabolism at the center of systemic disease etiology and intervention. By aligning future research with this perspective, we can move toward more durable and holistic strategies to combat the growing burden of metabolic and neurodegenerative disorders.

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Declaration of interests

No interests are declared.

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