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Glucose as a Metabolic Guardian of Neurons: Mechanistic Links Between Energy Homeostasis, Redox Defense, Ion Balance and Neurotransmission: A Narrative Review

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ABSTRACT

Neurons possess exceptionally high and continuous metabolic demands and depend predominantly on a reliable supply of glucose and oxygen to maintain electrical activity, synaptic transmission, ion gradients, neurotransmitter cycling and cellular integrity. Although glucose is traditionally regarded primarily as an energetic substrate, accumulating evidence indicates that neuronal glucose metabolism performs several interconnected functions that influence neuronal survival. Glucose-derived carbon supports glycolysis and mitochondrial oxidative phosphorylation for ATP generation, while diversion through the pentose-phosphate pathway (PPP) generates NADPH required for maintenance of the reduced glutathione pool and cellular redox homeostasis. Adequate ATP availability sustains Na^+/K^+-ATPase activity, calcium extrusion, vesicular neurotransmission and other energy-dependent processes, thereby limiting membrane depolarization and excitotoxic injury. Glucose metabolism is also closely coupled to astrocyte function, glutamate clearance and, under specific physiological and pathological conditions, lactate transfer between astrocytes and neurons. Conversely, insufficient glucose availability produces bioenergetic failure, ionic disequilibrium, oxidative stress and excitotoxicity, whereas chronic glucose excess is associated with oxidative stress, advanced glycation, mitochondrial dysfunction, neuroinflammation and impaired cerebral glucose metabolism. Importantly, the astrocyte–neuron lactate shuttle (ANLS) remains an area of active debate, and current evidence supports greater metabolic flexibility of neurons than originally proposed. This review integrates established and emerging evidence to propose a unified model in which adequate glucose availability supports neuronal survival through coordinated bioenergetic, antioxidant, ionic and neurotransmitter-related mechanisms, while both glucose deficiency and chronic excess can become injurious through distinct but convergent pathways.

Key words: Glucose metabolism; neurons; GLUT3; glycolysis; pentose-phosphate pathway; NADPH; glutathione; oxidative stress; ATP; Na^+/K^+-ATPase; excitotoxicity; astrocytes; lactate; neuroprotection.

1. Introduction

The mammalian brain has an exceptionally high energy requirement relative to its mass. Continuous neuronal signaling, maintenance of membrane potential, synaptic vesicle cycling, neurotransmitter recycling, axonal transport and macromolecular turnover require a sustained supply of metabolic energy. Glucose has therefore long been recognized as the major physiological fuel supporting cerebral metabolism. Importantly, glucose metabolism is not restricted to ATP generation; it also supplies carbon skeletons for biosynthesis and reducing equivalents required for cellular antioxidant defense [1].

Neuronal metabolism is particularly vulnerable to interruption because neurons have limited energy reserves and depend on continuous substrate availability. The close relationship between neuronal activity and glucose utilization reflects the high energetic cost of restoring ionic gradients and

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maintaining synaptic function [1,2]. At nerve terminals, ATP is required for ion homeostasis, calcium handling and synaptic-vesicle recycling [3].

The cellular entry and utilization of glucose are tightly regulated. Glucose crosses the blood–brain barrier primarily through glucose transporters, with GLUT1 playing a major role in delivery to the brain parenchyma and GLUT3 providing high-affinity glucose transport in neurons [1,4]. Once inside neurons, glucose can enter glycolysis, mitochondrial oxidative metabolism and the pentose-phosphate pathway (PPP), allowing one substrate to support several physiologically distinct functions.

The concept that glucose is simply an energy substrate, however, is incomplete. Glucose availability affects neuronal redox balance, membrane excitability, neurotransmitter homeostasis and susceptibility to oxidative and excitotoxic injury. The purpose of this review is to integrate these mechanisms and explain how physiological glucose metabolism can function as a fundamental determinant of neuronal resilience, while distinguishing this physiological role from the pathological consequences of glucose deficiency and chronic hyperglycemia.

2. Neuronal glucose uptake: the first step in metabolic protection

Glucose delivery to neural tissue is controlled by specialized facilitative glucose transporters. GLUT1 is highly expressed at the blood–brain barrier, whereas GLUT3 is particularly important for neuronal glucose uptake because of its high affinity for glucose [1,4]. This arrangement enables neurons to maintain glucose uptake over a relatively broad range of extracellular glucose concentrations.

GLUT3 is therefore more than a passive transporter: it represents an important component of neuronal metabolic adaptation. Changes in neuronal activity, metabolic demand and pathological conditions can influence GLUT3 expression and glucose utilization [4]. Recent reviews continue to identify GLUT1 and GLUT3 as major components of cerebral glucose delivery and neuronal glucose uptake, while emphasizing that glucose transport is dynamically altered during metabolic disease and neurological injury [4].

Once transported into neurons, glucose is phosphorylated to glucose-6-phosphate and enters several interconnected metabolic pathways. The subsequent partitioning of glucose-derived carbon is critical because glycolysis and mitochondrial oxidation primarily support energy production, whereas the PPP provides NADPH and biosynthetic intermediates [1,5].

3. Glucose-derived ATP: The energetic foundation of neuronal survival

Glucose undergoes glycolysis to generate pyruvate, ATP and reducing equivalents. Under aerobic conditions, pyruvate can enter mitochondria and undergo conversion to acetyl-CoA, followed by oxidation through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. This process produces a major fraction of the ATP required for neuronal activity [1,3].

The importance of glucose-derived ATP becomes particularly evident at synapses. Neurotransmission requires energy for synaptic-vesicle loading and recycling, maintenance of ion gradients, restoration of intracellular calcium concentrations and postsynaptic signaling [3]. Consequently, a reduction in glucose availability can rapidly compromise synaptic function.

One of the largest energy expenditures in the brain is associated with maintenance of transmembrane ion gradients. The neuronal Na^+/K^+-ATPase consumes ATP to export Na^+ and import K^+, thereby restoring ionic gradients following neuronal excitation [6]. The Na^+/K^+-ATPase is therefore an important link between glucose metabolism and neuronal electrical stability.

The sequence can be summarized as: Glucose → ATP → Na^+/K^+-ATPase activity → ionic-gradient maintenance → membrane stability. Failure of ATP production reduces pump activity, causing intracellular Na^+ accumulation, K^+ loss and membrane depolarization. These changes can further promote excessive Ca^{2+} influx and abnormal neurotransmitter release, establishing conditions that favor neuronal injury [1,3,6].

4. Glucose and the pentose-phosphate pathway: An antioxidant function

A major and sometimes underappreciated function of neuronal glucose metabolism is maintenance of redox homeostasis. The oxidative branch of the PPP converts glucose-6-phosphate into intermediates

while generating NADPH. NADPH is essential for maintaining antioxidant systems, particularly by supporting regeneration of reduced glutathione (GSH) from oxidized glutathione (GSSG) [5].
The pathway can therefore be represented as: Glucose → glucose-6-phosphate → PPP → NADPH → glutathione reductase → GSH → ROS detoxification. Neurons are especially sensitive to oxidative and nitrosative stress because of their high oxygen consumption, abundant membrane lipids and substantial metabolic activity. Experimental evidence has demonstrated that inhibition of the neuronal PPP increases susceptibility to glutathione oxidation and apoptotic death, whereas stimulation of PPP activity can improve resistance to nitrosative stress [5].

Quantitatively, only a modest fraction of neuronal glucose - on the order of a few percent under basal conditions — is thought to be routed through the oxidative PPP, yet flux-assessment studies indicate this contribution has likely been underestimated by standard ^{13}C-labeling approaches, in part because PPP-derived carbon re-enters glycolytic intermediates and is difficult to distinguish from direct glycolytic flux [19,20]. Direct measurement in functionally intact neurons confirms that PPP flux is quantitatively significant for redox and biosynthetic support even though it is smaller in magnitude than glycolytic flux [21]. Recent work has further emphasized the possibility that neuronal glucose may be preferentially routed through the PPP during periods of increased activity or oxidative challenge, generating NADPH for antioxidant defense while also providing metabolic intermediates that can re-enter glycolysis and contribute to energy production [7]. Thus, glucose metabolism can support neuronal survival through two complementary metabolic outputs: ATP production supporting bioenergetic and ion-homeostatic functions, and NADPH production supporting antioxidant capacity.

5. Glucose metabolism and calcium homeostasis

Calcium is essential for neuronal signaling but becomes toxic when intracellular concentrations remain excessively elevated. During neuronal excitation, voltage-gated calcium channels and glutamate receptors can increase intracellular Ca^{2+}. ATP-dependent systems subsequently restore intracellular calcium concentrations through plasma-membrane and intracellular calcium transport mechanisms.
Adequate glucose availability therefore indirectly contributes to calcium homeostasis by sustaining ATP production. Conversely, metabolic failure compromises ATP-dependent calcium extrusion and sequestration. The sequence can be summarized as: Glucose deficiency → ATP depletion → impaired ion pumps and Ca^{2+} handling → intracellular Ca^{2+} accumulation → mitochondrial dysfunction and ROS generation → neuronal injury. This relationship is particularly important during ischemia and severe hypoglycemia, when glucose availability becomes inadequate and energy failure develops rapidly [1,8].

This bioenergetic-excitotoxic coupling is not unique to hypoglycemia: an influential hypothesis holds that partial or chronic impairment of cellular energy metabolism can itself lower the threshold for excitotoxic neuronal death by leaving voltage-gated Mg^{2+} block of NMDA receptors incompletely relieved at resting potential while still permitting pathological Ca^{2+} entry upon receptor activation, providing a unifying mechanistic link between energy failure and excitotoxicity across several neurodegenerative contexts [22].

6. Glucose metabolism and prevention of excitotoxicity

Excitotoxicity represents a major pathway of neuronal injury associated with excessive glutamatergic signaling. Excessive activation of glutamate receptors, particularly NMDA receptors, can produce substantial Ca^{2+} influx and activate downstream pathways associated with oxidative stress, mitochondrial dysfunction, proteolysis and cell death.
Glutamate homeostasis itself is metabolically demanding. Astrocytes play a central role in removing glutamate from the extracellular space through high-affinity transport systems. This uptake is coupled to Na^+ transport and therefore increases the energetic requirement for maintaining intracellular ion gradients. Classical experimental work demonstrated that glutamate uptake into astrocytes stimulates glycolysis through a mechanism involving Na^+/K^+-ATPase activation [9].

Adequate glucose availability can therefore limit excitotoxicity indirectly by providing the energy required for Na^+/K^+-ATPase activity, glutamate uptake, membrane-potential maintenance and calcium regulation. Glucose is not itself an antagonist of excitotoxic receptors; rather, it supports the energy-dependent cellular systems that prevent excessive excitatory signaling from progressing to irreversible injury.

7. Astrocyte-neuron metabolic coupling

The relationship between glucose, astrocytes and neurons has generated substantial scientific interest. The astrocyte–neuron lactate shuttle (ANLS) hypothesis proposed that neuronal activity stimulates astrocytic glucose uptake and glycolysis, producing lactate that can subsequently be transferred to neurons and oxidized as an energy substrate [9,10]. Lactate can indeed serve as an oxidative substrate for neurons, and astrocytes and neurons express monocarboxylate transporters that can facilitate lactate transfer [10].

However, the extent to which lactate transfer represents an obligatory or quantitatively dominant pathway for neuronal energy metabolism remains controversial. Several studies and reviews argue that neurons can directly utilize glucose and possess substantial metabolic flexibility [11,12]. A stoichiometric analysis of the ANLS has raised specific quantitative objections, concluding that reported rates of astrocytic lactate production are insufficient to account for the energetic demands historically attributed to the shuttle [11]. Recent work further supports a model in which neuronal glucose utilization and lactate oxidation can coexist and the relative contribution of each substrate varies with physiological and pathological conditions, brain region and developmental stage [13].

Accordingly, the most defensible current interpretation is that astrocyte–neuron metabolic coupling provides an important supplementary and context-dependent mechanism of neuronal energy support, rather than replacing direct neuronal glucose utilization.

8. Glucose metabolism and neurotransmitter homeostasis

Neuronal communication depends on continuous synthesis, release, inactivation, recycling and resynthesis of neurotransmitters. These processes require substantial metabolic support. Glucose-derived carbon contributes to intermediary metabolism and provides precursors for synthesis of neurotransmitters and other neuroactive molecules [1]. At the same time, ATP generated through glucose metabolism powers neurotransmitter transport, synaptic vesicle cycling and ion-gradient restoration [3].

Glutamatergic neurotransmission provides a particularly important example of the relationship between metabolism and signaling. Glutamate released into the synaptic cleft must be rapidly cleared to prevent excessive receptor activation. Astrocytic uptake and subsequent conversion through the glutamate–glutamine cycle require energy and metabolic substrates [9]. Thus, glucose metabolism participates in neurotransmission at several levels: glucose → ATP → ion gradients → synaptic transmission; glucose → metabolic intermediates → neurotransmitter synthesis; and glucose → astrocyte energy metabolism → glutamate clearance → prevention of excitotoxicity.

9. Glucose deficiency and neuronal injury

The neuroprotective effects described above depend on adequate glucose availability. Severe glucose deficiency produces the opposite phenotype. During hypoglycemia or ischemia, ATP production falls as substrate availability becomes insufficient. Na^+/K^+-ATPase activity and other energy-dependent mechanisms become compromised, producing membrane depolarization, altered ion gradients and calcium dysregulation [1,8].

Hypoglycemic brain injury is particularly interesting because neuronal death cannot be explained simply by intracellular glucose starvation. Experimental studies have implicated excessive neuronal excitation and extracellular excitotoxic mechanisms in hypoglycemic neuronal injury [8]. Ischemia adds a second major limitation: reduced oxygen delivery. The simultaneous loss of glucose and oxygen produces rapid bioenergetic failure, mitochondrial dysfunction, ionic imbalance and oxidative stress; reperfusion may further intensify ROS production [14].

Therefore: Glucose deficiency → ↓ATP → ion-pump failure → depolarization/Ca^{2+} dysregulation → excitotoxicity + oxidative stress → neuronal injury.

10. Why excess glucose can also become harmful

The relationship between glucose and neuronal survival is not linear. While physiological glucose availability is essential, chronic glucose excess can promote pathological processes. Persistent hyperglycemia is associated with increased oxidative stress, altered glucose metabolism, mitochondrial dysfunction, inflammatory signaling and formation of advanced glycation end products (AGEs) [15,16].

Hyperglycemia can increase flux through several pathways, including the polyol and hexosamine pathways, alter protein kinase C signaling and promote nonenzymatic glycation. AGEs can interact with receptors including RAGE and contribute to inflammatory and oxidative signaling [15]. In diabetes, abnormalities in cerebral glucose transport and metabolism have been associated with impaired synaptic function and cognitive dysfunction, together with oxidative stress, inflammation, mitochondrial abnormalities and altered insulin signaling [16–18].

Thus, the biological relationship can be conceptualized as a metabolic optimum: insufficient glucose causes energy failure and excitotoxic injury; physiological glucose availability supports ATP production, redox maintenance, ion homeostasis and neurotransmission; and chronic glucose excess promotes oxidative stress, glycation, mitochondrial dysfunction and neuroinflammation. The key principle is therefore not that "more glucose protects neurons," but that appropriate glucose availability and regulated glucose metabolism are essential for neuronal homeostasis.

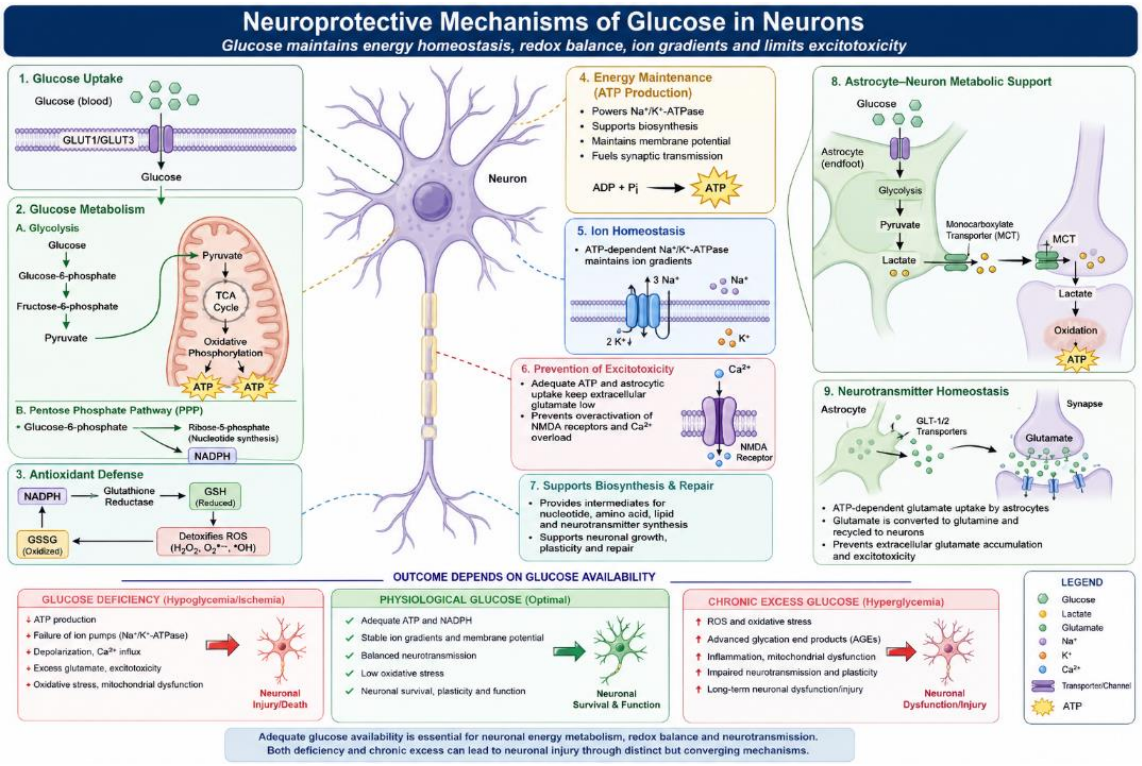


Figure 1. *Neuroprotective mechanisms of glucose in neurons. Glucose enters the brain through GLUT1-dependent transport and neurons through high-affinity GLUT3. Intracellular glucose supports glycolysis and mitochondrial ATP generation, while the pentose-phosphate pathway produces NADPH for glutathione-dependent antioxidant defense. ATP maintains Na^+/K^+-ATPase activity, calcium homeostasis and synaptic transmission. Astrocyte metabolism provides context-dependent lactate support, while energy-dependent glutamate uptake limits excitotoxicity. The lower panel contrasts glucose deficiency, physiological glucose availability and chronic excess. The figure is a conceptual synthesis of the cited literature and is not intended to imply that all pathways have identical quantitative contributions in every neuronal population.*

11. An integrated model of glucose-mediated neuronal protection

The available evidence supports an integrated model in which glucose metabolism influences neuronal survival through interconnected metabolic pathways (Figure 1). Glucose enters the brain through GLUT1-dependent transport at the blood–brain barrier and is taken up by neurons predominantly through high-affinity GLUT3. Intracellular glucose is distributed among glycolysis, mitochondrial oxidative metabolism and the pentose-phosphate pathway. Glycolytic and mitochondrial metabolism generate ATP, which supports Na^+/K^+-ATPase activity, calcium homeostasis, synaptic vesicle cycling and neurotransmission. PPP activity generates NADPH, which supports glutathione-dependent antioxidant defense. Astrocyte glucose metabolism additionally contributes to metabolic coupling with neurons through lactate under specific conditions. Adequate glucose availability therefore supports

energy metabolism, redox homeostasis, ion gradients and neurotransmitter balance. Glucose deficiency and chronic glucose excess produce distinct but convergent pathways of neuronal injury (Figure 2).

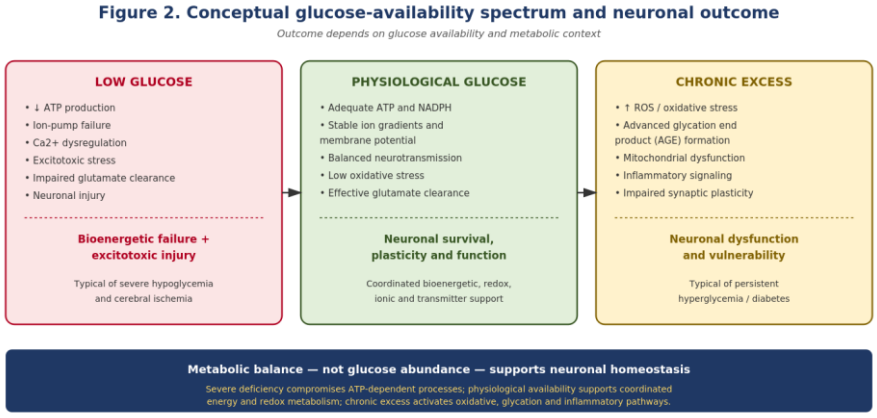


Figure 2. *Conceptual glucose-availability spectrum and neuronal outcome. The relationship between glucose availability and neuronal outcome is context dependent. Severe deficiency primarily compromises ATP-dependent processes and ionic homeostasis, physiological availability supports coordinated energy and redox metabolism, and chronic excess can activate oxidative, glycation and inflammatory pathways.*

12. Therapeutic and translational implications

Understanding glucose metabolism as a multidimensional determinant of neuronal survival has potential implications for neurological disease. Strategies that preserve physiological cerebral glucose delivery may be relevant to conditions characterized by impaired glucose transport or utilization. Selective enhancement of antioxidant pathways downstream of glucose metabolism, including NADPH-dependent systems, could potentially improve neuronal resilience to oxidative stress. Maintaining astrocyte metabolic competence may also support neuronal function during periods of high metabolic demand.

However, therapeutic manipulation of glucose metabolism must be approached cautiously. Increasing glucose availability indiscriminately is unlikely to be universally beneficial because chronic hyperglycemia can itself promote oxidative, inflammatory and glycation-related injury. Likewise, interventions directed at lactate metabolism should account for the substantial metabolic flexibility of neurons and the continuing debate concerning the quantitative contribution of the ANLS [11–13]. Future research should focus on cell-specific metabolic flux using stable-isotope tracing, genetically encoded metabolic sensors, single-cell metabolomics, spatial transcriptomics and *in vivo* imaging.

13. Limitations and unresolved questions

Several important questions remain unresolved. First, the relative contributions of direct neuronal glucose oxidation and astrocyte-derived lactate vary according to brain region, developmental state, neuronal activity and experimental conditions. Second, measurements of whole-brain glucose uptake cannot necessarily distinguish neuronal from astrocytic glucose utilization [1,11]. Third, cultured neurons and astrocytes may not reproduce the metabolic organization of the intact adult brain.

Although the PPP clearly contributes to neuronal antioxidant defense, the quantitative partitioning of glucose between glycolysis and the PPP during different physiological states remains incompletely defined, and standard isotope-tracing methods may systematically underestimate PPP flux in intact neurons [19,20]. Recent evidence supporting a substantial role for PPP flux during increased neuronal activity provides an important refinement but requires validation across different brain regions and experimental systems [7]. Finally, the consequences of glucose depend not only on concentration but also on duration, cellular compartment, metabolic flux, insulin signaling, mitochondrial function and the accompanying inflammatory and vascular environment.

14. Conclusion

Glucose should not be viewed merely as a fuel consumed by neurons. Rather, glucose metabolism constitutes a central biochemical network that supports neuronal energy production, antioxidant defense, ion homeostasis, neurotransmitter cycling and cellular maintenance. Through glycolysis and

mitochondrial oxidative phosphorylation, glucose provides ATP required for the energetically demanding processes underlying neuronal excitability and synaptic transmission. Through the pentose-phosphate pathway, glucose generates NADPH that contributes to maintenance of glutathione-dependent antioxidant defense. By sustaining ATP-dependent ion transport and neurotransmitter clearance, adequate glucose availability indirectly limits calcium dysregulation and excitotoxicity. Astrocyte-neuron metabolic coupling provides an additional layer of metabolic flexibility through lactate and other intermediates.

At the same time, neuronal protection depends on metabolic balance rather than glucose abundance. Severe glucose deficiency produces energy failure and excitotoxic injury, whereas chronic glucose excess can promote oxidative stress, glycation, mitochondrial dysfunction and neuroinflammation. Collectively, current evidence supports the concept of glucose as a metabolic guardian of neuronal homeostasis, provided that glucose availability and intracellular metabolism remain within a physiological range. Future therapeutic strategies should therefore aim not simply to increase or decrease glucose, but to preserve cell-specific glucose utilization, redox balance, mitochondrial function and neuron-glia metabolic coupling.

Table 1. Major glucose-dependent mechanisms contributing to neuronal homeostasis

Metabolic route/process	Principal output	Neuronal function	Potential consequence of failure
GLUT1/GLUT3-mediated glucose transport	Intracellular glucose	Substrate delivery for energy and biosynthesis	Reduced metabolic substrate availability
Glycolysis	ATP, pyruvate, NADH	Rapid ATP support; pyruvate supply	Energy deficit and impaired synaptic function
Mitochondrial oxidation	ATP, metabolic intermediates	Sustained energy production and cellular maintenance	ATP depletion, mitochondrial dysfunction
Pentose-phosphate pathway	NADPH, ribose-5-phosphate	Redox defense and biosynthesis	Oxidative/nitrosative stress susceptibility
Na^+/K^+-ATPase	Ion-gradient restoration	Membrane potential and excitability	Depolarization and ionic disequilibrium
Calcium handling	ATP-dependent extrusion/sequestration	Limits Ca^{2+} overload	Mitochondrial injury and cell death signaling
Astrocytic glucose/lactate metabolism	Lactate and metabolic support	Context-dependent metabolic coupling	Reduced metabolic flexibility
Glutamate clearance	Energy-dependent uptake/recycling	Limits excitotoxic receptor activation	Extracellular glutamate accumulation

The Table summarizes the principal ways in which glucose-derived metabolism contributes to neuronal function. The pathways are interconnected rather than independent; for example, ATP generated from glucose metabolism sustains ion pumps that in turn support neurotransmitter clearance and synaptic stability.

Table 2. Glucose availability states and predicted cellular consequences

State	Metabolic signature	Major cellular mechanisms	Expected neuronal phenotype
Severe deficiency / hypoglycemia	↓ glucose flux; ↓ ATP	Na^+/K^+-ATPase failure; depolarization; Ca^{2+} dysregulation; excitotoxicity	Acute dysfunction and possible neuronal injury
Ischemia	↓ glucose + ↓ oxygen	Bioenergetic failure; mitochondrial dysfunction; oxidative stress	Rapid neuronal injury; reperfusion-associated oxidative stress
Physiological availability	Balanced metabolic flux	ATP production; PPP-derived NADPH; ion and neurotransmitter homeostasis	Neuronal function, plasticity and survival
Chronic excess / hyperglycemia	↑ glucose flux and collateral pathways	ROS; AGEs/RAGE; polyol and hexosamine pathways; inflammation; mitochondrial stress	Chronic neuronal dysfunction and cognitive vulnerability

The Table is conceptual and does not define a single glucose concentration threshold applicable to all brain regions, experimental systems or disease states.

Table 3. Priority research questions for future studies

Question	Recommended approach
How is glucose partitioned between glycolysis, PPP and mitochondrial oxidation in active neurons?	Stable-isotope tracing combined with compartment-specific metabolomics
What is the quantitative contribution of astrocyte-derived lactate under different activity states?	*In vivo* isotope tracing, genetically encoded lactate sensors and cell-specific perturbation
How does chronic hyperglycemia alter neuronal glucose transport and redox metabolism?	Longitudinal imaging of GLUTs, NADPH/GSH and mitochondrial redox state
Which neuronal populations are most vulnerable to glucose metabolic disruption?	Single-cell/spatial transcriptomics integrated with metabolic phenotyping
Can redox-supportive pathways be targeted without increasing pathological glucose flux?	Cell-specific metabolic intervention and preclinical validation

Declarations

Much of the content provided herein is developed using AI tools, and is meant to help researchers who are working in the fields of neurological problems.

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Data availability: No new datasets were generated or analyzed.

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