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# Fueling the Mind: Brain Metabolism in Health and Neurodevelopmental Disorders

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## Abstract

The adult human brain, under resting conditions, consumes approximately 20% of total body glucose, a demand that is even higher during the first decade of life. The brain metabolic landscape is intricately regulated throughout development, and each cell type exhibits distinct metabolic signatures at each specific stage. This picture becomes even more intricate when considering that metabolism is dynamically modulated to sustain critical biological processes, such as cell proliferation and differentiation and synaptic activity–dependent processes. The orchestration between metabolic regulation and the aforementioned physiological processes often relies on metabolism-dependent changes in the epigenetic landscape, which shape gene expression patterns to trigger selected downstream biological responses. Perturbations of brain metabolic pathways are frequently the cause of severe neurodevelopmental disorders. This review explores the latest insights into the regulation of brain metabolism in health and disease.

## INTRODUCTION

The adult brain is the most energetic and metabolically demanding organ, with neuronal activity requiring most of its energy budget (23). The brain reallocates energy and metabolites from the whole organism to support its functions and optimizes available resources in a dynamic and cell-specific process (80). Despite several decades of research, many mechanisms underlying brain energy metabolism remain poorly understood, particularly those used during periods of heightened demand, such as brain development or intense synaptic activity. This knowledge gap arises from the intricate nature of the metabolic pathways; their compartmentalization within cellular regions; and the rapid, tightly regulated nature of biochemical reactions.

At the cellular level, metabolism plays a central role in regulating cell fate through various stages of development (69). Indeed, metabolic reprogramming is a crucial feature of cortical development, influencing neuronal proliferation, differentiation, and maturation (44, 50, 63, 75). These metabolic shifts also impact epigenetic regulation and synaptic activity, resulting in behavioral adaptations (21, 30, 71, 110) (**Figure 1**). In response to extrinsic or intrinsic stimuli, cells can reorganize their metabolic network to reallocate energy and metabolites, thereby supporting new physiological states. Emerging evidence suggests that metabolic shifts are not just reactive adaptations but also play an active role in development and synaptic plasticity (50).

As brain metabolism is fundamental for brain functions, disruption in energy homeostasis and metabolite supply or utilization during critical developmental windows can profoundly impact brain maturation and later functions. Indeed, impaired brain metabolism has been implicated in neurodevelopmental disorders (NDDs), either as a primary cause or as a significant contributing factor (10, 63, 67, 77). Inborn errors of metabolism exemplify conditions that arise from primary defects in brain energy homeostasis (79). However, in most cases, the metabolic disruptions are

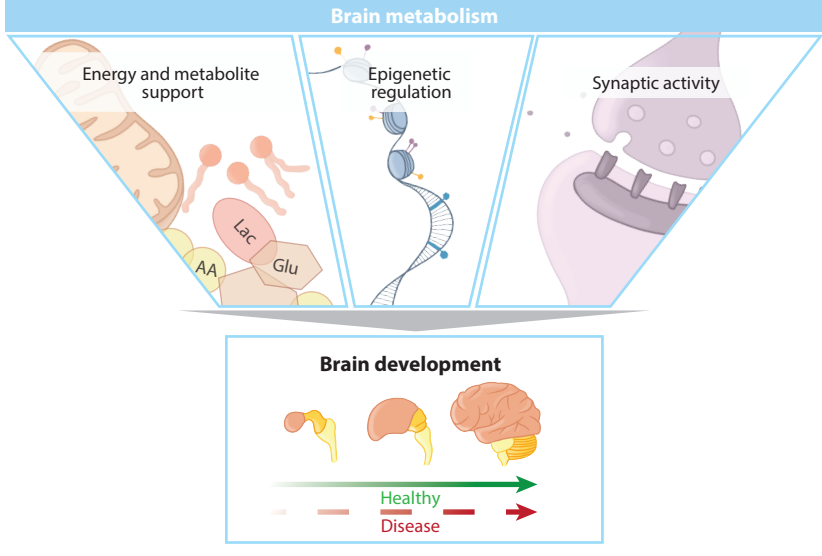


**Figure 1**

Metabolism plays a key role in brain development. Brain physiological functioning relies on the tight orchestration between different metabolic pathways. Several intermediates derived from cellular metabolic reactions constitute the building blocks of essential macromolecules and can shape the epigenetic landscape, ultimately modulating gene expression. Moreover, the energy produced through different metabolic routes sustains synaptic activity–dependent processes. Abbreviations: AA, amino acid; Glu, glucose; Lac, lactate.

not the primary cause but act as co-occurring factors that critically contribute to the disorder, as observed in conditions such as intellectual disabilities, autism spectrum disorder (ASD), and pediatric epilepsy (15, 34, 43, 79, 94, 112).

This review highlights recently identified metabolic processes that play a pivotal role in regulating key stages of brain development and synaptic functions. We also provide examples of NDDs in which disruptions in these metabolic mechanisms have recently been documented in the literature.

## GLUCOSE METABOLISM

Glucose is the brain's primary energy substrate, accounting for nearly 20% of the body's total glucose consumption (80). It fuels central carbon metabolism, entering glycolysis to produce adenosine triphosphate (ATP), pyruvate, or lactate during anaerobic respiration. Pyruvate is either converted into lactate or transported to mitochondria, where it generates acetyl-coenzyme A (acetyl-CoA) to drive the tricarboxylic acid (TCA) cycle and produce reduced nicotinamide adenine dinucleotide (NADH), which is in turn used for oxidative phosphorylation (OXPHOS) and ATP production. Despite glucose's central role throughout the lifespan, its usage differs between embryonic development and adulthood.

### Embryonic Stage

During embryonic brain development, glucose is predominantly directed toward highly proliferative and undifferentiated neural stem cells (NSCs), which rely heavily on anaerobic glycolysis. While less energy efficient, this metabolic modality favors biosynthetic pathways critical for rapid cell division and growth. As neural stem and progenitor cells (NSPCs) differentiate and mature into neurons, they undergo a metabolic shift, transitioning from anaerobic glycolysis to OXPHOS and the pentose phosphate pathway (PPP). This shift reflects the evolving role of glucose, from supporting early NSPC proliferation to sustaining neuronal activity and synaptic transmission in mature neurons. This mechanism is well-conserved across species (44, 57) and accompanied by changes in mitochondrial morphology, biogenesis, and activity (2, 31, 33, 50, 118), as discussed in the section titled Mitochondrial Dynamics at the Crossroads of Neural Progenitor Proliferation and Differentiation.

Although the mechanisms driving this metabolic shift are not fully understood, recent studies have identified novel regulators. For example, in *Drosophila* during the larval and the pupal stages, neuroblasts asymmetrically divide into a daughter cell with stem cell identity and a smaller daughter cell committed to differentiation. The steroid hormone ecdysone, a key regulator of the larva-to-pupa transition, induces metabolic changes in neuroblasts, promoting increased OXPHOS rate, cell cycle exit, and neural fate commitment. The Mediator complex has been identified as a critical link between steroid hormone signaling, energy metabolism, and cell proliferation. Mediator, in response to ecdysone, drives the changes in metabolic enzyme activity that ultimately lead to neuroblast cell cycle exit (44).

Similarly, in mammals, during neurulation—the process in which the neural tube closes to form the neuroepithelium from the neuroectoderm—neural progenitors shift from glycolysis to OXPHOS metabolism as they differentiate into neurons. The transcription factor Myc, already known for regulating proliferative states and self-renewal, is a key regulator of this transition. High *MYC* expression levels in human embryonic stem cells and in the neuroectoderm maintain a high glycolytic state during proliferation. The downregulation of *MYC* during neuroepithelium formation orchestrates changes in mitochondrial morphology and maturation (17, 31, 37).

Emerging evidence suggests that metabolic switches are bidirectional and actively drive key processes regulating development. Indeed, neural differentiation induces a shift to OXPHOS

metabolism and is promoted by glycolysis inhibition. For instance, in mammals, the TP53-inducible glycolysis and apoptosis regulator (TIGAR) previously associated with tumor growth has been recently implicated in regulating the balance between NSC proliferation and differentiation. Acting as an endogenous glycolysis inhibitor, TIGAR is gradually upregulated during cortical development, promoting NSC differentiation into neurons (119). Conversely, inhibition of OXPHOS in the mouse embryonic cortex disrupts the balance between NSC proliferation and differentiation, impairing proper development (58). Genetic disruption of the apoptosis-inducing factor, a mitochondrial protein essential for the respiratory chain, leads to increased glycolytic flux, enhanced NSC proliferation, and reduced neural differentiation (58).

## Postnatal Stage

As brain cells mature and fully differentiate, their metabolic profiles become specialized. In the adult brain, neurons and astrocytes exhibit complementary metabolic adaptations (12). Astrocytes predominantly rely on glycolysis, while neurons exhibit low glycolytic rates and instead utilize OXPHOS and the PPP (41). This metabolic compartmentalization is efficiently achieved by regulating the enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (Pfkfb3) in neurons and astrocytes (41). Pfkfb3 catalyzes the generation of fructose-2,6-bisphosphate (46), a potent activator of 6-phosphofructo-1-kinase (Pfk1) (113), a master regulator of glycolysis (111). Evidence on rat cortical primary cultures has shown that Pfkfb3 levels are low in neurons due to its continuous degradation by the E3 ubiquitin ligase anaphase-promoting complex (APC/C) (41). By contrast, astrocytes exhibit low APC/C activity, leading to Pfkfb3 stabilization and accumulation, which makes these cells highly glycolytic (41).

It has long been known that by sustaining high glycolytic rates, astrocytes can efficiently produce considerable amounts of lactate, which is then released into the extracellular space and used by neurons as a preferential energy source. Neurons can convert lactate into pyruvate, which is further oxidized through the TCA and OXPHOS pathways with high energy yields (8). According to this astrocyte-neuron lactate shuttle model, astrocytes can sustain high glycolytic rates because they express efficient antioxidant systems, which are less abundant in neurons (47, 66, 82, 104). Consequently, to maintain their antioxidant status, neurons tightly limit their glycolytic rates and instead prioritize the PPP, a crucial metabolic route for the regeneration of reduced glutathione (9, 41, 62). Indeed, the induction of high glycolytic rates in neurons can cause detrimental effects on neuronal functioning. For instance, in a mouse model overexpressing Pfkfb3 under a neuron-specific promoter during the adult stage, the enhanced glycolytic rates led to reduced PPP activity, oxidative stress, impaired mitochondrial function, and disrupted lipid metabolism. Multiple behavioral impairments, including increased anxiety and cognitive deficits, accompanied these metabolic derangements (55).

Increasing evidence suggests that neurons exhibit flexibility in their metabolic strategies during defined postnatal stages and under specific conditions (21, 84). For example, while neurons in the adult brain seem to rely mainly on the lactate produced by astrocytes, during the juvenile stage, they appear capable of actively metabolizing glucose, in addition to lactate, to meet their energy demands (21, 84, 110). Moreover, hippocampal neurons during the juvenile stage express Pfkfb3, and perturbation of its function during this time window leads to long-term memory formation defects, suggesting that neuronal glycolysis is critically required during the juvenile stage (21). This regulation could represent a metabolic adaptation to sustain the higher brain energy needs during the juvenile stage, which has also been described in humans (16, 21). This hypothesis is further supported by gene expression analyses in the hippocampus of juvenile and adult rats, which revealed that the younger animals exhibit higher expression of genes involved in virtually

all glucose metabolic pathways, including glycolysis, TCA, the PPP, and glycogen metabolism, which are indicative of high energy demands (21). Moreover, the levels of endothelial cell glucose transporter 1 (GLUT1), which is expressed in the endothelial cells of the blood vessels (29), were found to be higher in the juvenile hippocampi, suggesting more efficient glucose uptake from the blood compared to adult hippocampi (21). Juvenile hippocampi also exhibited increased expression of GLUT3, a neuron-specific glucose transporter (6, 105), whereas the levels of glial GLUT1 (29) were lower. This expression pattern was accompanied by higher extracellular glucose levels in the juvenile hippocampi under basal conditions, whereas lactate levels were comparable between juvenile and adult stages (21). These findings suggest that glucose transport into neurons is higher in the juvenile hippocampus than in the adult hippocampus, which likely prioritizes glucose delivery to astrocytes and oligodendrocytes. Moreover, the neurons in the juvenile hippocampus appear capable of efficiently metabolizing glucose and lactate to meet their heightened metabolic demands. By contrast, the adult hippocampus seems to rely more on astrocytic lactate utilization.

Recent findings suggest that metabolic heterogeneity extends across diverse neuronal subtypes during the postnatal stage. For example, the fast-spiking parvalbumin (PV+) interneurons (22, 42, 45) need a considerable amount of energy to generate high-frequency trains of action potentials. PV+ neuron maturation includes the development of specialized metabolic features, such as a higher mitochondrial number compared to other neuronal populations and the expression of specific genes linked to mitochondrial function (38, 74). Experiments carried out in mouse brain suggested that the terminal differentiation of PV+ interneurons is triggered by synaptic activity during the postnatal stage and that their metabolic identity is established by a molecular network involving peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), estrogen-related receptor gamma (ERRγ), and myocyte-specific enhancer factor 2c (Mef2c) (74). As a key regulator of mitochondrial biogenesis and energy metabolism, PGC-1α is essential for the higher mitochondrial enrichment and the establishment of the gene expression patterns that characterize adult PV+ neurons. These findings suggest that PGC-1α could support both the metabolic and electrophysiological maturation of PV+ interneurons, enabling their high-frequency firing (74).

Given the remarkable diversity of neuronal subtypes in the mammalian brain, each characterized by distinct firing patterns (18, 61), the hypothesis that each cell type may also exhibit a unique metabolic signature is reasonable. Nevertheless, our current understanding of such metabolic diversity remains incomplete.

## Glucose Metabolism and Neurological Disorders

Disruption of glucose homeostasis during brain development has severe consequences, often leading to severe neurodevelopmental diseases.

For example, pyruvate dehydrogenase (PDH) complex mutations cause a human medical condition known as pyruvate dehydrogenase deficiency (PDHD). Under physiological conditions, PDH catalyzes the conversion of pyruvate, produced by glycolysis, into acetyl-CoA. This step allows the further oxidation of pyruvate via the TCA cycle and OXPHOS, resulting in ATP production. In this context, PDHD is characterized by aberrant pyruvate and lactate accumulation in plasma and urine, ATP deficiency, and impaired development and function of various tissues, particularly the brain. PDHD clinical manifestations include a broad spectrum of symptoms ranging from moderate neurological impairments to severe brain malformations at birth, often accompanied by epilepsy (10). Mouse models with brain-specific reductions in PDH activity mirror key features of the human disease, such as cerebral hypotrophy, neuronal cell loss, and epilepsy, accompanied by decreased TCA cycle flux in the brain and impaired synaptic transmission (51, 67,

87). Recent studies combining isotope tracing and in vivo brain imaging revealed increased glucose uptake and utilization in PDHD mouse brains, with the glucose oxidation route interrupted at the PDH level (67). Interestingly, some neurological and metabolic dysfunctions in PDHD mutant mice could be improved with alternative carbon sources. For example, acetate supplementation bypasses the defective PDH reaction and fuels the TCA cycle (51). Similarly, succinyl-CoA, synthesized from propionate in PDH-deficient glial cells, acts as an additional substrate for the TCA cycle. Remarkably, oral administration of propionate, along with a ketogenic diet, has extended the lifespan of PDHD mice and improved certain molecular and behavioral phenotypes, suggesting promising potential for therapeutic applications (67).

Increasing evidence suggests that the maternal metabolic environment also plays a role during embryonic brain development. Maternal diabetes, for example, is a risk factor for embryonic lethality and neural tube closure defects in offspring (68). Studies suggest that hyperglycemia during pregnancy inhibits cellular proliferation and induces neuroepithelium senescence (116). Moderate maternal hyperglycemia, which does not result in neural tube defects, can still lead to altered DNA methylation patterns in offspring. These epigenetic changes disrupt cortical development by prematurely differentiating NSCs during early neurogenesis (53).

Impaired glucose metabolism also affects the maturation of radial glia. In rodent models, hyperglycemia has been shown to disrupt the ability of radial glia to form the scaffold necessary for proper neural migration during corticogenesis. Excess glucose impaired intracellular calcium signaling and mitochondrial transport. These disruptions led to delayed neurogenesis, hindered proper neuronal migration, and compromised adult brain connectivity (93). NDDs, such as ASD and cognitive disorders, have also been associated with gestational diabetes (68, 98). While their relationship remains unclear, multiple molecular and cellular mechanisms might contribute to the pathology, including defects in bioenergetics, epigenetic regulation, cortical migration, and connectivity (7, 20).

## MITOCHONDRIAL DYNAMICS AT THE CROSSROADS OF NEURAL PROGENITOR PROLIFERATION AND DIFFERENTIATION

Mitochondria are essential organelles that play multifaceted roles, functioning as key regulators of energy production, metabolic signaling, and cellular homeostasis.

In mature neurons, mitochondria are critical regulators of neuroplasticity, supporting synaptogenesis and dendritic spine growth. Moreover, mitochondria can sense calcium fluctuations associated with synaptic activity and dynamically adjust ATP synthesis locally at synapses to meet the heightened energy demands imposed by synaptic transmission (35, 91, 92). Recent evidence suggests that these processes involve the tethering of mitochondria to the dendritic spines (5, 91), the mitochondrial calcium uniporter (MCU) (3), and the malate-aspartate shuttle (MAS) (84), among others, depending on fuel availability, as further discussed in the section titled Cellular Metabolism Fuels Synaptic Transmission.

However, in addition to the pivotal roles of the mitochondria in energy production and redox-based signaling, recent research underscores the significance of mitochondrial dynamics—including fission and fusion—as critical metabolic switches driving brain development.

As previously mentioned, during embryonic development, NSCs predominantly rely on glycolytic metabolism, transitioning to mitochondrial OXPHOS as differentiation proceeds. This metabolic reprogramming aligns with increased ATP production, enhanced activity of the PPP, and increased levels of TCA cycle intermediates that drive neuronal development (28, 72, 73, 103).

Although this mitochondrial metabolic shift is conserved across species (1, 44, 48, 50, 75), recent studies revealed that the pace of mitochondrial maturation—encompassing activity and

dynamics—dictates the timing of cortical neural maturation. These properties are species specific (48). For instance, in vitro studies have shown that while mitochondrial maturation in mouse cortical neurons requires 3 to 4 weeks, this process in human cortical neurons takes several months. This slower pace in humans is mirrored by delayed mitochondrial oxidative activity compared to mice. Furthermore, genetic and pharmacological manipulations that enhance mitochondrial oxygen consumption and activity in human neurons accelerate their development. Conversely, reducing the metabolic rate in mouse neurons delays their maturation (48). These findings highlight the interplay between mitochondrial metabolism and the timing of neural differentiation.

Mitochondrial maturation is finely interconnected with their shape and dynamics. Indeed, mitochondria exhibit distinct morphologies at different stages of neural development and under specific physiological states. They are elongated in uncommitted NSCs, fragmented and low in number and size in committed neural progenitors and newborn neurons, and acquire a more elongated and wider shape during neural differentiation and maturation (49, 50, 58). Changes in mitochondrial shape during embryonic development have been shown to drive neurogenesis, from regulating the balance between NSC self-renewal and neural fate commitment to synaptogenesis. For instance, loss of mitochondrial fusion in *Drosophila* neuroblasts due to depletion of Optic atrophy 1 (Opa1), a mitochondrial inner membrane protein, leads to a reduction in mature intermediate progenitors and young neurons (28). Similarly, increasing fission and mitochondrial fragmentation by loss of Mitofusin 1 (MFN1) and MFN2 in NSC in the mammalian system promotes their commitment to neural differentiation and maturation (58). In addition, the impaired mitochondrial dynamics upon MFN1/MFN2 loss in NSCs alters adult hippocampal neurogenesis, ultimately resulting in learning and memory deficits (58). Interestingly, recent evidence has highlighted a specific postmitotic period of fate plasticity during which mitochondrial dynamics play a pivotal role in guiding cell fate. Manipulating mitochondrial dynamics during mouse and human cortical neurogenesis, combined with monitoring cell cycle progression, has shown that increased mitochondrial fission promotes neuronal differentiation. By contrast, inducing mitochondrial fusion after mitosis redirects daughter cells toward self-renewal (49). The downstream molecular drivers of these effects remain incompletely explored. One candidate is Sirtuin 1 (Sirt1), a member of the class III histone deacetylase (HDAC) family that has been shown to sense mitochondrial oxidative status and, upon activation, to induce chromatin remodeling via deacetylation of lysine 16 of histone H4, promoting neural fate determination (49).

The link between mitochondrial dysfunction and abnormal NSC proliferation and brain development is further highlighted by primary microcephaly caused by mutations in genes involved in mitochondrial function and metabolism, such as *Microcephalin 1* (*MCPH1*) and the *solute carrier family 25 member 19* (*SLC25A19*). *MCPH1* is highly expressed in NSCs and radial glia (56). Although its primary role is maintaining genomic integrity (65), a recent study indicated that it is involved in the crosstalk between mitochondrial energetic pathways and NSC proliferation and survival (56). In mouse neural progenitors, *Mcph1* regulates their symmetric division, and its deletion is sufficient to recapitulate the microcephalic phenotype observed in patients. Notably, the MCPH1 protein localizes to mitochondria, where it interacts with voltage-dependent anion channel 1 (VDAC1), an ion channel in the mitochondrial outer membrane, ensuring proper mitochondrial calcium influx. Mutations in *MCPH1* impair mitochondrial function, leading to mitochondrial fragmentation, aberrant NSC proliferation, and ultimately microcephaly (56). The *SLC25A19* gene encodes a thiamine pyrophosphate carrier, a coenzyme critical for the α-ketoglutarate dehydrogenase complex participating in the TCA cycle. Mutations in *SLC25A19* disrupt mitochondrial respiration, NADH homeostasis, amino acid metabolism, and TCA cycle activity, ultimately affecting NSC proliferation during cortical development (54). Mitochondrial dysfunction, manifested in the abnormal activities of the electron transport chain and

impaired energy metabolism, is increasingly recognized as a contributing factor in NDDs, often caused by genes not directly associated with mitochondrial functionality (43, 59, 78, 96, 97). Whether mitochondrial dysfunctions are merely a consequence of pathological events or represent a common denominator and critical driver of NDD pathogenesis remains under investigation.

## AMINO ACIDS IN THE BRAIN: ANOTHER ENERGY SOURCE

While it is well-established that glucose serves as the primary energy source in the brain, neurons may utilize alternative energy sources during specific developmental stages (63, 76). For instance, by integrating genetic approaches with comprehensive omics analyses, our group has shown that during the early postnatal period, neurons in the cerebral cortex significantly rely on the utilization of branched-chain amino acids (BCAAs) for energy (63).

BCAAs—valine, leucine, and isoleucine—belong to the group of large neutral amino acids (LNAAs) and are essential amino acids. Thus, mammals need to acquire them from their diet. A BCAA supply is particularly crucial for the brain, which relies on a constant influx of BCAAs from the bloodstream (63, 77, 109). BCAA metabolism in the brain is tightly regulated, and a precise balance between intake and breakdown is essential. In physiological conditions, the branched-chain ketoacid dehydrogenase kinase (BCKDK) modulates the branched-chain ketoacid dehydrogenase (BCKDH) complex, which catalyzes the irreversible, rate-limiting step in the BCAA catabolism (40). Inactivating mutations in the *BCKDK* gene impair this regulatory mechanism, leading to excessive BCKDH activity and decreased BCAA levels (77). In humans, homozygous loss-of-function mutations in *BCKDK* cause a Mendelian form of ASD, accompanied by intellectual disability and epilepsy (77). Similarly, *Bckdk*-knockout mice exhibit diverse neurological abnormalities, including epileptic seizures, tremors, and hindlimb clasping, which can be alleviated by dietary BCAA supplementation (77), indicating that *BCKDK* mutation–related conditions can potentially be treated by restoring normal BCAA levels (108).

Similar to patients with *BCKDK* deficiency, individuals with homozygous mutations in the gene encoding the LNAA transporter LAT1 exhibit severe neurological symptoms (63, 109). LAT1, encoded by the *solute carrier family 7 member 5* (*SLC7A5*) gene, is expressed at the blood-brain barrier (BBB) and in immature neurons, where it facilitates the import of LNAAs, including the BCAAs (117). In mice, deletion of *Slc7a5* in the endothelial cells of blood vessels and the BBB leads to an abnormal brain amino acid profile, locomotion deficits, autism-related behaviors, and a synaptic excitation-inhibition imbalance. Interestingly, some neurobehavioral abnormalities observed in these *Slc7a5* mutants could be rescued by intracerebroventricular administration of leucine and isoleucine during adulthood (109). BCAAs appear to play a crucial role in energy production in immature neurons. Indeed, mice lacking LAT1 in immature neurons prioritize mitochondrial BCAA catabolism for energy production over cytoplasmic BCAA catabolic pathways. Since under physiological conditions several enzymes involved in mitochondrial BCAA metabolism also participate in fatty acid (FA) β-oxidation, an intracellular drop in BCAA levels caused by *Slc7a5* dysfunction triggers a compensatory upregulation of several enzymes shared between the lipid and BCAA pathways, which in turn boosts FA β-oxidation. These findings suggest that, during the perinatal period, neurons rely heavily on BCAAs as key substrates for ATP production. In their absence, FAs are diverted toward the β-oxidation pathway instead of being utilized for glycerophospholipid synthesis (63).

At the cellular level, the loss of *Slc7a5* in neurons induces cell-autonomous changes in neuronal firing, rendering these cells more prone to apoptosis during the critical period of cortical circuit refinement in the perinatal phase (11, 63). Remarkably, disruption of *Slc7a5* function during this

particular developmental window results in long-lasting behavioral changes, with affected mice exhibiting moderate motor deficits and signs of impaired sociability and social memory (63).

## CELLULAR METABOLISM FUELS SYNAPTIC TRANSMISSION

A considerable amount of energy produced in the brain is spent to support fast and sustained responses underlying synaptic activity. These include—but are not limited to—the generation and propagation of action potentials, the neurotransmitter loading in presynaptic vesicles, the reversal of the ionic gradients underlying postsynaptic responses, and neurotransmitter reuptake and recycling (12). Furthermore, activity-dependent processes, such as memory formation, activate specific transcriptional programs (60) and require de novo messenger RNA (mRNA) translation (26), increasing energy demands.

Given this, a strong connection between synaptic activity and metabolic regulation is essential. This coupling is achieved through the coordinated actions of diverse brain cell types and may involve different molecular mechanisms, depending on the specific developmental stage and fuel availability.

Neurons are capable of synthesizing ATP locally at synapses, and this process is crucial for maintaining physiological synaptic function. In this frame, neurons stimulated by applying defined bursts of electrical activity in vitro exhibit only minor fluctuations in ATP levels. However, when ATP synthesis is inhibited during stimulation, ATP levels decline drastically, indicating that ATP production is dynamically regulated according to synaptic activity rates to meet the higher energy demands (90).

In 1994, Pellerin & Magistretti (83) proposed that the coupling between synaptic activity and energy supply could involve a glutamate-astrocyte signaling pathway. According to this model, known as the astrocyte-neuron lactate shuttle, the glutamate released at excitatory synapses can be taken up by astrocytes and cotransported with sodium. This flux leads to an increased intracellular concentration of sodium, which stimulates the activation of the sodium/potassium ATPase, ATP consumption, and glucose uptake and utilization. The increased glycolytic rates triggered in astrocytes result in a consequent production of lactate, which is then released into the extracellular space, where neurons can use it as a readily available energy source to meet the high energy demands imposed by synaptic activity. This mechanism enables astrocytes to sense the neighboring neurons' activity and adjust their metabolic rates accordingly (83). Over the past three decades, this model has been refined. For example, recent research supporting the neuron-astrocyte-coupling model has highlighted the critical role of adenosine signaling in linking neuronal and astrocytic metabolism during synaptic activity (110). Specifically, adenosine released during synaptic activity (114) binds to the astrocytic adenosine A2b receptor, which in turn activates the cyclic adenosine 3′,5′-monophosphate (cAMP)–protein kinase A (PKA) signaling pathway, thereby stimulating glycolysis in astrocytes and the release of lactate into the extracellular space (**Figure 2**).

Perturbation of the astrocytic A2b receptor signaling pathway in vivo leads to defective synaptic transmission, impaired long-term potentiation induction in the hippocampus, recognition memory defects, and impaired sleep/wake regulation. Interestingly, some of the electrophysiological phenotypes observed in acute brain slices after A2b receptor perturbation could be rescued by lactate supplementation (110). Altogether, these data suggest that adenosine–A2b receptor signaling could be an additional mechanism through which the neuronal activity stimulates astrocyte metabolism and are in line with the finding that the transport of lactate from astrocytes to neurons is necessary for memory formation in the adult rat hippocampus (26).

The metabolic coupling between neurons and their neighboring astrocytes also protects neurons from lipid-mediated toxicity during periods of intense neuronal activity (47). Reactive oxygen

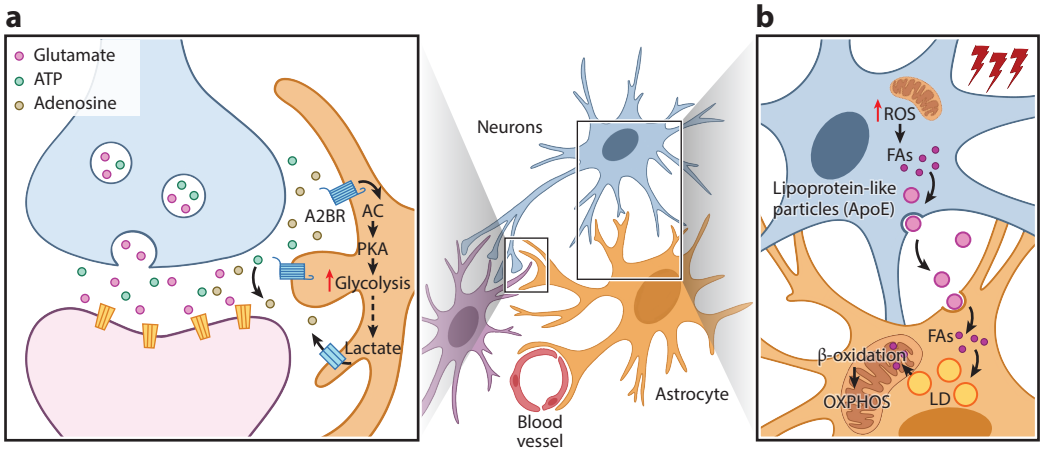


**Figure 2**

Astrocyte-neuron metabolic coupling during synaptic activity. (*a*) The ATP released by synaptic vesicles is hydrolyzed into adenosine in the extracellular space. Adenosine binds A2BR on the astrocytic membrane, thereby stimulating the AC-PKA signaling pathway. These events lead to increased glycolytic rates and lactate release from astrocytes. Panel *a* adapted from Reference 110 (CC BY 4.0). (*b*) Enhanced synaptic activity causes increased production of ROS in neurons, leading to the formation of peroxidized lipids. The peroxidized lipids are broken down into FAs, which in turn are packaged into lipid-rich particles containing ApoE. These lipid-rich particles are secreted by neurons and internalized by astrocytes, where they are converted into FAs, stored as LDs, and then metabolized through the β-oxidation pathway. Data for panel *b* from Reference 47. Abbreviations: A2BR, adenosine A2b receptor; AC, adenylyl cyclase; ATP, adenosine triphosphate; FA, fatty acid; LD, lipid droplet; OXPHOS, oxidative phosphorylation; PKA, protein kinase A; ROS, reactive oxygen species.

species generated in neurons during enhanced synaptic activity lead to the increased formation of peroxidized lipids (47), which, if not efficiently removed, can have detrimental effects on neuronal function (106). According to a recently proposed model, neurons respond to excitotoxicity by increasing autophagy rates to eliminate damaged membranes that may contain peroxidized lipids (47) (**Figure 2**). The peroxidized lipids are transferred to lysosomes through the autophagy pathway, where they are broken down into free FAs by lysosomal lipases. Since neurons have a limited capacity to degrade FAs via mitochondrial β-oxidation (102), removing FAs from the neuronal cytoplasm is crucial to avoid toxicity. To eliminate FAs, neurons package them into lipid-rich particles within the endoplasmic reticulum and secrete them through the secretory pathway (47). These lipid-rich particles, also containing ApoE, a component of high-density lipoprotein (HDL)-like particles (88), are then internalized by astrocytes, where they are stored as lipid droplets (47) (**Figure 2**). In parallel, the *N*-methyl-D-aspartate (NMDA) released by hyperactive neurons stimulates astrocytic NMDA receptors, triggering the breakdown of these lipid droplets into FAs by cytoplasmic lipases. These FAs are then metabolized via astrocytic β-oxidation, thereby preventing lipid accumulation and protecting neuronal integrity (47).

While it is true that lactate produced by astrocytes is an essential source of energy for neurons, recent evidence suggests that neurons themselves can also metabolize glucose through the glycolytic pathway during activity-dependent processes (21, 84). In in vitro cortical neurons using only glucose as fuel, synaptic activity stimulates glucose uptake from the external medium, increases neuronal respiration rates, and enhances neuronal glycolysis, leading to a concomitant rise in intracellular pyruvate and lactate levels (84). This activity-dependent stimulation of glycolysis appears to rely on cytoplasmic calcium signals generated during synaptic activity (4, 99). Cytoplasmic calcium activates Aralar, a component of the MAS, which facilitates aspartate-glutamate

exchange upon calcium binding (81, 84). Through the MAS, neurons can transfer reducing equivalents from the cytosol to the mitochondria to fuel OXPHOS. At the same time, this mechanism enables the regeneration of cytosolic $NAD^+$ (13), which is essential for glycolysis.

According to this model, Aralar promotes cytosolic $NAD^+$ regeneration, sustaining glycolytic glucose consumption and subsequent pyruvate production. This pyruvate is then utilized in mitochondria to fuel OXPHOS. This process represents a feedforward mechanism through which neurons can couple synaptic activity with energy production (84).

Interestingly, when neurons are cultured in vitro under oxidative conditions, using only lactate and pyruvate as energy substrates, the activity-driven ATP synthesis seems to rely on the mitochondrial calcium uptake family member 3 (MICU3) protein, which promotes calcium influx into mitochondria through the MCU, accelerating ATP production (3). These findings support the notion that neurons can utilize diverse metabolic pathways, depending on the availability of various energy substrates.

The role of neuronal glycolysis in synaptic activity in vivo is supported by a recent study in rats undergoing an inhibitory avoidance paradigm (21). In juvenile rats, the learning process induced a decrease in lactate levels in the hippocampus, accompanied by a gradual increase in glucose concentration. Moreover, the learning-induced rise in glucose levels was associated with higher expression of endothelial GLUT1 and neuronal GLUT3, indicating enhanced glucose transport from the blood to the hippocampal interstitium and increased neuronal glucose delivery. GLUT3 knockdown in the juvenile hippocampus resulted in defects in long-term memory formation, thus highlighting the critical role of neuronal glucose transport and metabolism in memory formation at this developmental stage (21). Furthermore, the formation of contextual memory led to an increase in Pfkfb3 expression. By contrast, APC/C levels showed the opposite trend in both neurons and astrocytes, indicating an activity-dependent glycolytic boost in both cell types. Notably, global or neuron-specific perturbation of Pfkfb3 function in the hippocampus impaired long-term memory formation in juvenile rats. This supports the idea that neuronal glycolysis is critical during this developmental stage (21).

## CELLULAR METABOLISM SHAPES THE EPIGENETIC LANDSCAPE IN THE BRAIN

It is well-established that the deposition of epigenetic modifications relies on the availability of specific cellular metabolites, which can serve as donor groups, cofactors, or inhibitors for the enzymes involved in remodeling the epigenetic landscape (25). For example, S-adenosylmethionine, synthesized from methionine, serves as the universal methyl group donor for DNA, RNA, and histone methylation. Moreover, the activity of some DNA and histone demethylases depends on the availability of α-ketoglutarate, while HDACs require $NAD^+$ (25) and are inhibited by beta-hydroxybutyrate (BHB) (76). Among the metabolites connecting metabolism to epigenetic regulation, acetyl-CoA is particularly noteworthy. Beyond its well-known roles in cellular metabolism, acetyl-CoA donates acetyl groups for protein acetylation, including that of histones. Acetyl-CoA can be generated through multiple metabolic pathways, such as glycolysis, β-oxidation, and BCAA catabolism (86).

Another possible acetyl-CoA biosynthetic pathway involves the acyl-CoA synthetase short-chain family member 2 (ACSS2) enzyme, which catalyzes the ATP-dependent conversion of acetate into acetyl-CoA. The newly synthesized acetyl-CoA is then used by histone acetyltransferases (HATs) to mediate histone acetylation (71, 86) (**Figure 3**). During in vitro neuronal differentiation, the knockdown of *Acss2* impairs the induction of neuronal genes, indicating that ACSS2-derived acetyl-CoA plays a pivotal role in orchestrating the transcriptional program

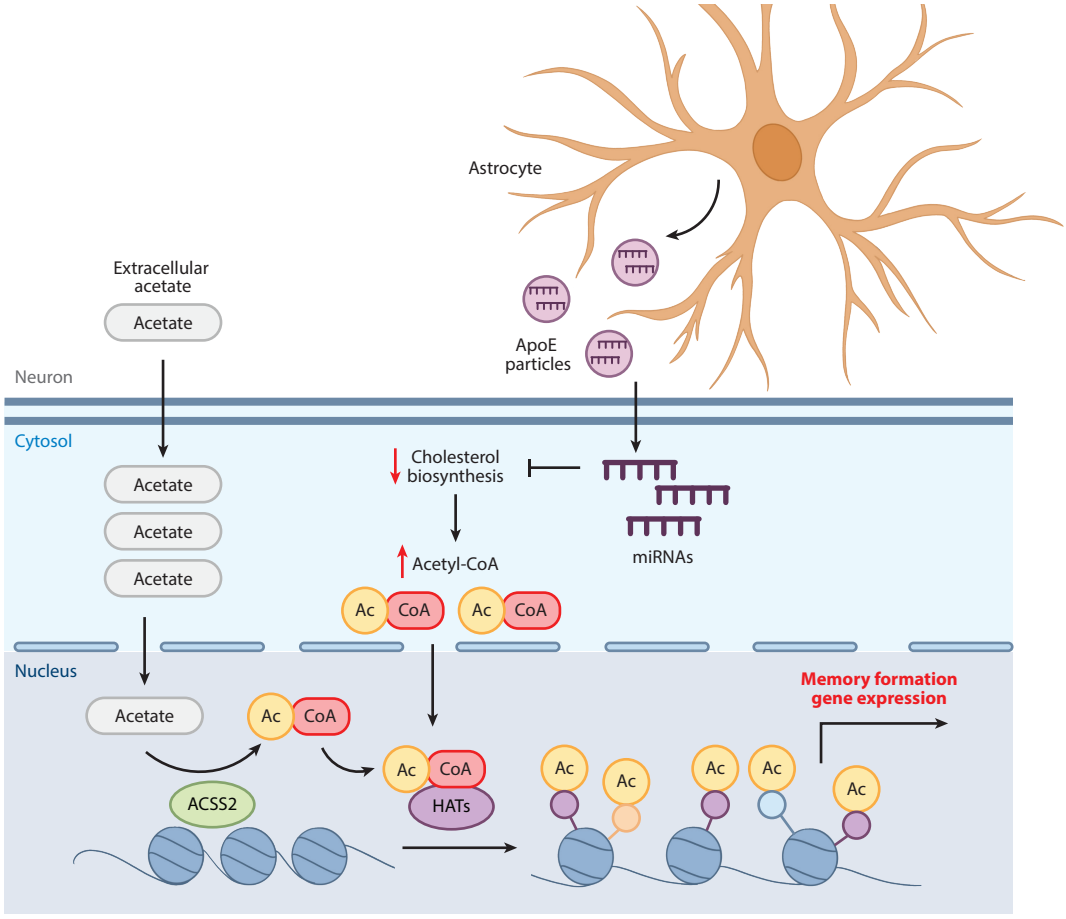


**Figure 3**

Cellular metabolism shapes the epigenetic landscape and modulates gene expression. (*Left*) Extracellular acetate can enter the neuronal nuclei, where it is converted into acetyl-CoA by ACSS2. Acetyl-CoA, in turn, is used by HATs to mediate histone acetylation and promote memory-related gene expression. Data from References 70 and 71. (*Right*) Astrocytes release ApoE particles containing miRNAs that mediate the suppression of the cholesterol biosynthetic pathway. This event leads to an increased accumulation of acetyl-CoA, which is used by HATs to acetylate the histones and enhance the expression of genes involved in memory formation. Data from Reference 64. Abbreviations: Ac, acetyl group; acetyl-CoA, acetyl-coenzyme A; ACSS2, acyl-CoA synthetase short-chain family member 2; HAT, histone acetyltransferase; miRNA, microRNA.

underlying this process (70). In the mouse hippocampus, ACSS2 and acetylation of histone H3 lysine 9 (H3K9ac) peaks overlap on a genome-wide scale, and the genes coenriched for both factors tend to show higher expression levels, including those involved in memory formation (**Figure 3**). Accordingly, *Acss2* knockdown in the dorsal hippocampus leads to impaired long-term spatial memory, attributed to aberrant gene expression (70). These findings suggest that ACSS2 enrichment at specific genomic regions promotes local nuclear acetyl-CoA production, which HATs can immediately use to acetylate histones and activate gene expression. Since acetyl-CoA is a key metabolic intermediate, this mechanism strongly connects the cell's metabolic state and gene regulation (70).

However, the binding of ACSS2 to chromatin increases cellular susceptibility to elevated acetate levels (71), a condition that can arise in humans following alcohol consumption (89). Stable

isotope–labeling experiments in mice have shown that alcohol metabolism increases acetate levels in the brain, including the prefrontal cortex and hippocampus. This acetate is readily incorporated into histones through the action of ACSS2. The alcohol-induced rise in histone acetylation levels in the hippocampus enhances the expression of several key neuronal genes, including those involved in synaptic function (71) (**Figure 3**). Additionally, behavioral studies suggested that alcohol-induced histone acetylation and altered gene expression may contribute to the formation of contextual memories associated with alcohol consumption (71), which are potent triggers for alcohol-seeking behavior, cravings, and relapse in humans (52). Notably, many of the molecular and behavioral changes observed in wild-type mice following alcohol exposure were reversed by perturbing ACSS2 function.

It is worth noting that exposure of pregnant mice to alcohol resulted in the incorporation of alcohol-derived acetyl groups into the developing fetal midbrain and forebrain (71). The ability of alcohol to potentially shape the epigenetic landscape of the developing fetal brain might play a role in the pathogenesis of fetal alcohol spectrum disorder (FASD), a human medical condition caused by prenatal alcohol exposure and characterized by growth retardation, developmental delay, and abnormal brain development and function (95).

Recent studies suggest that astrocytes might modulate neuronal acetyl-CoA levels and histone acetylation dynamics via ApoE (64). In vitro experiments showed that astrocyte-released ApoE particles can deliver microRNAs (miRNAs) to neurons, thereby inducing posttranscriptional silencing of cholesterol biosynthetic genes (64). This results in the accumulation of acetyl-CoA, which is utilized for histone acetylation. Chromatin immunoprecipitation experiments followed by sequencing (ChIP-seq) revealed ApoE-mediated regulation of histone acetylation across several genomic regions, including regulatory elements of key memory-related genes (**Figure 3**). In vivo, *ApoE* knockdown reduces dendritic spine density and neuronal dendritic complexity and causes learning and memory defects (64). At the molecular level, contextual fear conditioning, a paradigm used to assess hippocampal memory formation in mouse models (85), induced high histone acetylation levels at immediate early genes (IEGs) in control mice. By contrast, *ApoE*-knockdown mice exhibited lower acetyl-CoA levels, drastically reduced histone acetylation, and lower IEG expression compared to control mice undergoing the same task (64). Collectively, these findings suggest that astrocytes, through ApoE-mediated miRNA delivery, may ensure adequate suppression of neuronal cholesterol biosynthesis, allowing neurons to maintain a sufficient pool of acetyl-CoA that can be used for the activity-dependent deposition of histone acetylation marks. This mechanism aligns with previous studies showing that de novo cholesterol biosynthesis in neurons is essential during embryonic development (101) yet becomes dispensable in adulthood, when neurons can rely on cholesterol supplied by neighboring astrocytes (32).

During periods of nutrient scarcity, such as fasting, tissues can utilize alternative energy sources, such as ketone bodies, which are small molecules derived from lipid catabolism. Ketone bodies are generated from acetyl-CoA, initially converted into acetoacetate through the sequential action of various enzymes. Subsequently, acetoacetate can be further transformed into acetone or BHB (76).

A recent study reported an increase in beta-hydroxybutyrylation of histone H3 lysine 9 (H3K9-BHB) in the livers and cerebral cortices of mice after 48 h of fasting. ChIP-seq analyses revealed that fasting-induced H3K9-BHB was primarily enriched at promoters and enhancers in both tissues, with additional enrichment in intergenic genomic regions of the cortex. The presence of fasting-induced H3K9-BHB correlated with increased gene expression in both the liver and cortex. Interestingly, in both tissues, genes involved in circadian rhythm regulation exhibited higher H3K9-BHB enrichment and increased expression following fasting. In the cortex, fasting enhanced H3K9-BHB levels and the expression of genes associated with synaptic transmission and metabolism. These findings suggest that fasting, through BHB production and

subsequent H3K9-BHB formation, may modulate gene expression to optimize energy utilization in both neuronal and nonneuronal brain cells (19).

Among the posttranslational modifications shaped by cellular metabolism, lysine lactylation (Klac) in histone and nonhistone proteins has gained significant attention recently. In the adult mouse brain, Klac levels increase upon chronic and systemic lactate administration. This phenomenon has also been observed in neuronal primary cultures in a dose-dependent manner. Double immunostaining analyses revealed that in the mouse brain, Klac is present in diverse cell types, including neurons, astrocytes, and microglia, suggesting that this modification could occur ubiquitously in neural cells. At the cellular level, immunohistochemistry analyses performed in neuronal primary cultures revealed that the signal was spread across the nucleus, the cytoplasm, and neurites, which suggested that several proteins residing in diverse cellular compartments can be modified by the lactylation of lysine residues (39).

Another posttranslational modification influenced by cellular metabolism is lysine crotonylation (Kcr), which is dependent on the levels of the short-chain fatty acid crotonate (100). Kcr and Klac are widely distributed in the fetal brain and dynamically regulated during embryonic development (25). Multiomics chromatin and gene expression profiling revealed that genes exhibiting the combined high enrichment of H3K9ac, crotonylation of histone H3 lysine 9 (H3K9cr), and lactylation of histone H3 lysine 18 (H3K18lac) show increased chromatin accessibility and higher expression levels, thus suggesting that the combination of these epigenetic modifications can mark transcriptionally active regions (24). Moreover, genes more enriched in H3K9ac and H3K9cr in the developing telencephalon were involved in RNA and protein metabolism, whereas those with higher levels of H3K18lac were primarily involved in regulating cell proliferation, in line with the observed decrease in H3K18lac levels as neurogenesis progresses (24).

These findings suggest that the establishment of histone acetylation, crotonylation, and lactylation is finely tuned during embryonic brain development, even at the single-amino-acid-residue level, each of which can be modified by adding different chemical groups. Given that the developing brain undergoes a significant remodeling of its metabolic landscape and available cellular metabolites (63), it is likely that the epigenetic landscape is similarly shaped to drive the specific gene expression patterns underlying neurodevelopment.

Since Klac is sensitive to cellular lactate levels and neuronal activity, as discussed in the previous sections, is tightly related to lactate production, it is not surprising that synaptic activity might also impact Klac. Neuronal activation, both in vitro in primary cell cultures and in vivo upon electroconvulsive stimulation in mice, leads to an increased lactate production, which correlates with an increased Klac rate (39). By using social defeat stress (SDS) as a model of chronic stress in mice (36), Hagihara et al. (39) found higher brain lactate levels in defeated mice (mice subjected to SDS), and this was accompanied by an increased abundance of Klac in the prefrontal cortex. Of note, the extent of Klac positively correlated with the degree of phenotypic impairment observed after SDS. Moreover, the lactylation of diverse proteins was changed upon SDS, with some showing higher lactylation levels and others being less lactylated after the treatment, in partial contrast with the increased global Klac rates. Among the proteins with enhanced lactylation levels were nucleosome-related factors and histones, such as histone H1. However, the authors didn't analyze the genomic distribution of lactylated histone H1; therefore, whether the change in the H1 lactylation levels plays a role in chromatin regulation upon SDS remains unknown (39).

Altered lactate levels, both elevated and reduced, have been observed in various brain disorders, including depression, epilepsy, diabetic encephalopathy, schizophrenia, and bipolar disorder. However, the exact role of lactate (and lactate-dependent protein lactylation) in neurological conditions remains controversial, and whether lactate is harmful, has a neuroprotective effect, or plays no significant role in the pathogenesis of these disorders remains unclear (14, 27, 115).

Although not related to epigenetic modifications, in this context, it is worth mentioning a recent study that further emphasized the intrinsic interconnection between protein posttranslational modifications and metabolism. Recent evidence suggests that cellular glycolytic rates can modulate cytoskeleton dynamics and functions through the reversible lactylation of the α-tubulin protein. An assay performed in vitro revealed that, upon treatment with different concentrations of lactate or glucose, the α-tubulin lactylation levels increase in a dose-dependent manner (107). Moreover, α-tubulin lactylation levels are higher after the induction of hypoxia and are, in contrast, reduced upon glucose deprivation. These results suggested that α-tubulin lactylation relies on glucose catabolism, particularly glycolysis. In the mouse cerebral cortex, α-tubulin acetyltransferase 1 (MEC-17) and HDAC6 seem to be the enzymes responsible for the establishment of α-tubulin lactylation, with HDAC6 being the major player. In vitro assays showed that Sirt2 catalyzes α-tubulin delactylation in a $NAD^+$-dependent manner.

In cultured neurons, α-tubulin lactylation enhances neurite outgrowth and branching and promotes axonal regeneration after injury (107). Considering the metabolic reprogramming that occurs during neurodevelopment (63), the lactate-dependent regulation of cytoskeleton dynamics through the lactylation of α-tubulin could constitute a mechanism to shape neuronal morphology as cellular metabolism changes (107).

## CONCLUSIONS AND FUTURE PERSPECTIVES

The brain serves as the central command hub of an organism. It is responsible for processing and integrating information derived from both internal and external stimuli, thereby shaping the behavior and regulating the functioning of the organs accordingly.

Brain functions are underpinned by a metabolic program that is developmentally regulated and cell-type specific. Brain metabolism has evolved to accommodate even the most energetically demanding physiological processes, such as synaptic transmission. Furthermore, the availability of key cellular metabolites can shape the epigenetic landscape, ultimately regulating various essential downstream physiological processes according to the cellular metabolic state.

Despite significant advancements in our understanding of neuronal energy metabolism, critical questions remain unanswered, underscoring the need for further exploration. An important challenge lies in developing tools capable of capturing the dynamic metabolic changes that occur throughout development and in response to environmental or physiological stimuli. These tools must achieve single-cell resolution to unravel metabolic diversity at cellular and subcellular levels. In neurons, such diversity may manifest not only between individual cells but also within distinct compartments, such as the somata and axon terminals. Investigating these compartment-specific metabolic differences promises to revolutionize our understanding of neuronal function and energy homeostasis.

Addressing these open questions and leveraging emerging technologies will lead to a deeper understanding of neuronal metabolism, potentially leading to novel strategies for addressing NDDs and other metabolic diseases.

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