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Glucose metabolic crosstalk and regulation in brain function and diseases

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Abstract

Brain glucose metabolism, including glycolysis, the pentose phosphate pathway, and glycogen turnover, produces ATP for energetic support and provides the precursors for the synthesis of biological macromolecules. Although glucose metabolism in neurons and astrocytes has been extensively studied, the glucose metabolism of microglia and oligodendrocytes, and their interactions with neurons and astrocytes, remain critical to understand brain function. Brain regions with heterogeneous cell composition and cell-type-specific profiles of glucose metabolism suggest that metabolic networks within the brain are complex. Signal transduction proteins including those in the Wnt, GSK-3β, PI3K-AKT, and AMPK pathways are involved in regulating these networks. Additionally, glycolytic enzymes and metabolites, such as hexokinase 2, acetyl-CoA, and enolase 2, are implicated in the modulation of cellular function, microglial activation, glycation, and acetylation of biomolecules. Given these extensive networks, glucose metabolism dysfunction in the whole brain or specific cell types is strongly associated with

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neurologic pathology including ischemic brain injury and neurodegenerative disorders. This review characterizes the glucose metabolism networks of the brain based on molecular signaling and cellular and regional interactions, and elucidates glucose metabolism-based mechanisms of neurological diseases and therapeutic approaches that may ameliorate metabolic abnormalities in those diseases.

Keywords

glucose metabolism; brain; glycolysis; signal regulation; neurological disease

1 Introduction

Glucose is the primary energy source of the brain, which accounts for about 20% of whole-body glucose consumption (Jais *et al.*, 2016; Zhang *et al.*, 2014). Alternate fuel sources supporting the brain include ketone bodies (acetoacetate, and β-hydroxybutyrate), lactate, fatty acids, and amino acids (valine, glutamine, leucine, isoleucine), which are primarily used in settings of limited glucose availability, such as fasting, starvation, and extended exercise (Fig. 1) (Bowman *et al.*, 2019; Camandola and Mattson, 2017; Qi *et al.*, 2019; Schönfeld and Reiser, 2017). Brain glucose metabolism can produce adenosine triphosphate (ATP) to fulfill complex neurological functions, including neuronal signaling transmission (action potentials, synaptic transmission, glutamate cycling, etc.), which consumes 70% of the brain's energy, and non-signaling activities (resting potentials, axonal transport, mitochondrial proton leak, oligonucleotide turnover, actin cytoskeleton remodeling, etc.), using 30% of ATP produced from brain glucose metabolism (Fig. 1). Moreover, the carbon in the glucose structure can be transmitted to metabolites, such as pyruvate and glyceraldehyde-3-phosphate, which contribute to the synthesis of nucleic acids, fatty acids, and amino acids (Dienel, 2019). Glucose metabolism is also involved in oxidative stress modulation ($NADH/NAD^+$ and $NADP^+/NADPH$) (Fig. 1) (Dienel, 2019; Yu *et al.*, 2018). A growing literature base shows that glucose metabolites and metabolism-related enzymes, such as hexokinase, acetyl-CoA, and glycolytic enzyme glyceradehyde-3-phosphate dehydrogenase, can also directly participate in cellular signaling and functional regulation (Li *et al.*, 2018; Nakajima *et al.*, 2015; Sivanand *et al.*, 2018). For instance, lactate acts as a messenger modulating multiple molecular targets (hydroxycarboxylic acid receptor 1, acid-sensing ion channel, $NADH/NAD^+$ ratio, ATP-sensitive potassium channel, etc.) (Barros, 2013). In addition, the reduced ratio of NADH and NAD^+ resulting from glucose metabolism in microglia can suppress the inflammatory cascade (Shen *et al.*, 2017). Therefore, glucose metabolites not only support ATP production and supply the carbon for macromolecule synthesis, but also modulate various functions of neurons and glial cells.

Glucose entrance into the brain is controlled by a family of specific glucose transporters (GLUTs) via facilitated diffusion, and it has been demonstrated that serum glucose levels can be five-fold higher than levels in the brain (Hwang *et al.*, 2017; Hwang *et al.*, 2019). GLUT distribution in the vascular endothelial cells (ECs) of the blood-brain barrier (GLUT1), neurons (GLUT3,4,6,8), astrocytes (GLUT1,2), and microglia (GLUT 1, 3, 4, 5, 6, 8, 9, 10, 12, and 13) contribute to glucose transport from blood to cells in the brain (Fig.

2) (Wang *et al.*, 2019b; Zhang *et al.*, 2014), and GLUT-mediated glucose control is pivotal for cerebral metabolism.

The hypothalamus and pituitary play important roles maintaining blood glucose homeostasis, with some involvement of the cortex and striatum as well (Cheah and Amiel, 2012; Ter Horst *et al.*, 2018). The glucose-sensing neurons of the brain, parasympathetic (vagus) and sympathetic nerves, and peripheral organs, such as the liver, muscles, intestines, and pancreas, work together to regulate whole-body glucose metabolism (Duncan *et al.*, 2019; Soty *et al.*, 2017; Steinbusch *et al.*, 2015; Tan *et al.*, 2020a). Additionally, insulin receptors are widely expressed in the cerebral cortex, hippocampus, hypothalamus, thalamus, choroid plexus and cerebellum (Fernandez and Torres-Alemán, 2012). Therefore, the brain plays an important role in regulating peripheral glucose metabolism. In turn, systemic metabolic disorders caused by high fat diets can decrease brain glucose uptake by downregulating GLUT1 expression on the vascular endothelial cells. This response can be countered by the compensatory production of vascular endothelial growth factor, which helps to block obesity-associated neurodegeneration (Jais *et al.*, 2016). Ultimately, brain glucose metabolism and systemic glucose metabolism work in concert, and both brain and systemic metabolic disorders can contribute to the development of neurological disease.

Disturbances of glucose metabolism occur in the early stages of neurological disorders, catastrophically in stroke, and more subtly in Alzheimer's disease (AD) and Parkinson's disease (PD) (Camandola and Mattson, 2017; Putzu *et al.*, 2018). In the early reperfusion in a rat model of stroke, elevated glucose levels are observed in the infarct areas (Zhang *et al.*, 2016). In the brain of AD patients and AD mouse models, glucose utilization is reduced, particularly in the brain regions most affected by the disease (Camandola and Mattson, 2017; Zhou *et al.*, 2018b). Other evidence suggests that impaired glucose metabolism or disruption of cerebral insulin action contributes to the degeneration of neurons in AD (Camandola and Mattson, 2017; Kleinridders *et al.*, 2014; Yan *et al.*, 2020). Advances in methods for analyzing cell-type-specific features of glucose metabolism indicate that the metabolic alterations of glial cells strongly influence neuronal metabolism and regulate neurological function (Barros *et al.*, 2018b), suggesting that metabolic coupling between neurons and glia is important for normal brain function and that alterations in such coupling may contribute to the pathogenesis of neurodegenerative disorders.

The present review provides an overview of the important technologies for studying brain glucose metabolism and illustrates progress and remaining challenges regarding the role of glucose metabolism in neurological diseases. We highlight the heterogeneity of glucose metabolism among different cell populations in the brain and how such cell type-specific features of glucose metabolism may affect neuronal vulnerability. We then consider the intercellular metabolic networks involved in brain glucose metabolism. Understanding these networks and their involvement in intercellular signaling may reveal novel approaches for preventing and treating neurological disorders.

2 Glucose metabolism in the brain

2.1 Glucose metabolism for ATP generation

Cellular glucose is metabolized in the processes of glycolysis (including lactate production and oxidative phosphorylation), the pentose phosphate pathway (PPP), and glycogenesis (Fig. 3), which are critical to support cell function and energy storage (Mulukutla *et al.*, 2016). Under the presence of adequate oxygen, glucose enters into the oxidative phosphorylation pathway, while 10–15% of glucose is metabolized into carbon dioxide and water via an oxygen-independent process termed aerobic glycolysis (Shannon *et al.*, 2016; Vaishnavi *et al.*, 2010). Aerobic glycolysis is involved in multiple functions including biosynthesis, synaptic plasticity, synapse formation, and neurite growth (Goyal *et al.*, 2014; Shannon *et al.*, 2016).

2.2. Glucose metabolism in different brain regions

Positron emission tomography (PET) has identified areas of low glucose metabolism (amygdala, hippocampus, enthorinal cortex, parahippocampus, ventral diecncephalon, temporal poles), medium glucose metabolism (cerebellum, thalamus, caudate, nucleus accumbens, globus pallidus), and high glucose metabolism (putamen, remaining cortical regions) in the adult human brain (>18 years) (Tomasi *et al.*, 2017). In resting human brains (20–33 years old), aerobic glycolysis is used at the highest levels in the prefrontal cortices, medial and lateral parietal cortex, and lowest levels in the cerebellum and medial temporal lobes (Vaishnavi *et al.*, 2010). Brain aerobic glycolysis increases in childhood, reaching the peak at 5 years old, and gradually declines to lower levels at a mean age of 21, which persists with aging (Goyal *et al.*, 2014). Loss of brain aerobic glycolysis is related to human aging and Alzheimer's disease (Goyal *et al.*, 2017; Vlassenko and Raichle, 2015).

In addition to regional differences in the levels of glucose metabolism, it has also been noted that different regions of the brain may rely on different mechanisms of glucose metabolism. In rodents, the PPP is the primary mechanism of glucose metabolism in oligodendrocytes of the thalamus with low ATP/adenosine diphosphate (ADP) ratios, while glycolysis is the primary mechanism in the cortex and hippocampus with high ATP/ADP ratios (Kleinridders *et al.*, 2018). Additionally, fasting promotes lactate production in the cortex and hippocampus, which does not occur in the thalamus, hypothalamus, or amygdala (Kleinridders *et al.*, 2018).

In awake rats, 80% of energy expenditure in white matter is used for non-signaling processes, while 70% of energy expenditure in gray matter is utilized for signaling processes (Yu *et al.*, 2018). A higher activity rate of ATPase in the gray matter, compared to white matter, is conducive to this energetic support (Hyder and Rothman, 2017). Ultimately, different cell types with distinct characteristics of glucose metabolism contribute to metabolic heterogeneity in specific brain regions.

2.3. Glucose metabolism in brain cells

The mammalian brain has a complex anatomical structure, multiple cell types, and a multitude of signaling pathways that regulate neuronal network activity and neuroplasticity.

The main types of cells in the brain are neurons, astrocytes, oligodendrocytes, and microglia (Allen and Lyons, 2018). Moreover, there are subpopulations of neurons and glial cells that exhibit distinct morphological, molecular, and functional features (Davie *et al.*, 2018; Mu *et al.*, 2019). Various cell types and their cellular interconnections form intricate neural networks with complex mechanisms of glucose metabolism.

2.3.1. Glucose metabolism in neurons and astrocytes—In the resting, awake rat, excitatory neurons, inhibitory neurons, and glial cells utilize 27%, 22%, and 47% of energy respectively for non-signaling processes, such as housekeeping and resting potentials (Yu *et al.*, 2018). The energetic demands of specific cellular processes are estimated at 50% for synaptic transmission, 10–15% for action potentials, and 9–18% for other signaling-related processes, such as calcium responses and glutamate/GABA recycling in neurons (Yu *et al.*, 2018).

Glucose metabolism in neurons and astrocytes exhibits a compartmentalized pattern, which may be related to different enzymatic actions. Neurons have higher levels of hexokinase expression than astrocytes, therefore glucose is taken up preferentially by neurons (Lundgaard *et al.*, 2015). Astrocytes can come in contact with vasculature via their endfeet, facilitating their glucose uptake. Additionally, glucose-6-phosphatase-β, specifically expressed in the endoplasmic reticulum (ER) of astrocytes, cooperates with glucose-6-phosphate translocase, transferring glucose-6-phosphate from the cytosol to the ER, and allowing for the rapid uptake of glucose by astrocytes and delivery of glucose from astrocytes to neurons (Muller *et al.*, 2018; Pellerin, 2018). Glucose primarily undergoes anaerobic glycolysis in astrocytes due to higher levels of lactate dehydrogenase (LDH) compared to neurons. In contrast, neurons utilize oxidative phosphorylation as primary glucose metabolism (Halim *et al.*, 2010). Additionally, mitochondrial complex I in neurons can conjugate with complex III to form supercomplexes that allow for mitochondrial respiration, while most mitochondrial complex I is free in astrocytes, blocking glucose oxidative phosphorylation (Lopez-Fabuel *et al.*, 2016). The different enzymatic activity of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB) in neurons and astrocytes also contributes to the cellular diversity of glucose metabolism. PFKFB has four isoforms, and isoform 3 (PFKFB3) has the highest enzymatic activity contributing to the generation of fructose-2,6-bisphosphate. Although the gene expression of PFKFB3 in neurons and astrocytes is similar, neurons have lower levels of available PFKFB3 than astrocytes due to rapid neuronal degradation of the enzyme (Bolaños *et al.*, 2010). As a result of this difference, neurons undergo spontaneous apoptosis in the setting of mitochondrial dysfunction due to insufficient ATP production. In contrast, astrocytes can maintain energy production by rapid glycolysis via the upregulation of PFKFB, making them more resistant to mitochondrial dysfunction (Almeida *et al.*, 2001; Bolaños *et al.*, 2010). The PPP in neurons has an antioxidant function due to the production of $NADPH(H^+)$, a required factor for reduced glutathione generation (Bolaños *et al.*, 2010). Overexpression of PFKFB3 in neurons promotes oxidative stress and cellular injury, because the increase in glycolysis inhibits the PPP and the production of reduced glutathione (Herrero-Mendez *et al.*, 2009).

In summary: (1) Astrocytes have a higher affinity for glucose uptake and rapid glucose processing than neurons; (2) Astrocytes primarily utilize anaerobic metabolism of glucose and produce lactate; (3) Neurons primarily utilize oxidative phosphorylation of glucose.

2.3.2. Astrocyte-neuron energy interaction—The astrocyte-neuron lactate shuttle (ANLS) hypothesis suggests that astrocytes convert more glucose to lactate after stimulation by glutamate released from neurons (Bélanger *et al.*, 2011). The released lactate then serves as an energy source for the neighboring neurons (Fig. 4) (Bélanger *et al.*, 2011). Genetically encoded fluorescence resonance energy transfer utilizing the lactate sensor *Laconic,* in combination with *in vivo* two-photon laser scanning microscopy, identified higher levels of lactate in astrocytes compared to neurons, validating the concept that this lactate gradient is important for a carrier-mediated lactate flux from astrocytes to neurons (Fig. 4) (Machler *et al.*, 2016). However, the ANLS hypothesis is limited in its ability to explain the brain's response to the metabolic challenge of activation. Under rapid stimulation, mitochondrial metabolism may not be the primary mechanism for neuronal ATP production, due to the number of enzymatic steps required for oxidative phosphorylation (Díaz-García *et al.*, 2017). Rather, in settings of high activity, neurons have increased glucose consumption and produce lactate for energy demand predominantly via glycolysis, which does not depend on external lactate from astrocytes (Díaz-García *et al.*, 2017; Patel *et al.*, 2014).

To better understand the role of lactate in the brain, it is important to understand lactate metabolism and transport between neurons and astrocytes. The LDH-1 isoform, primarily expressed in neurons, oxidizes lactate to pyruvate, while the LDH-5 isoform is expressed in astrocytes and promotes the conversion of pyruvate to lactate (Fig. 4). Despite their distinct distribution, LDH-1 and LDH-5 do not directly modulate the lactate flow between neurons and astrocytes (Bak and Schousboe, 2017; Machler *et al.*, 2016). Connexin 43 and 30, the primary astroglial gap-junction proteins, allow for intercellular trafficking of energetic metabolites among astrocytes, blood vessels, and neurons (Rouach *et al.*, 2008). Monocarboxylate transporters (MCTs) are a family of transmembrane proteins (Perez-Escuredo *et al.*, 2016). In the brain, MCT1 is expressed exclusively in the vascular endothelial cells, ependymocytes, oligodendrocytes, and astrocytes. MCT2 is expressed on neuronal membranes (Suzuki *et al.*, 2011). MCT4 receptors are specifically expressed in astrocytes. MCT1, MCT2, and MCT4 contribute to the intracellular flow of lactate, pyruvate, and ketone bodies with a varying affinity (MCT2 > MCT1 >> MCT4) across plasma membranes according to concentration gradients (Perez-Escuredo *et al.*, 2016). Inhibition of either MCT1, MCT2, or MCT4 expression in the hippocampus leads to severely impaired long-term memory formation in rats. Providing exogenous lactate can rescue this memory impairment in MCT1 or MCT4 deficient rats, but not under MCT2 inhibition, which suggests the flow of lactate from glial cells to neurons is a critical function (Suzuki *et al.*, 2011).

In summary, the astrocytes near blood vessels can obtain glucose and convert it to lactate, which can then be shuttled into neurons for energy production.

2.3.3. Glycogen metabolism in astrocytes—Glycogen granules are distributed in the cell bodies of astrocytes, where they are concentrated near adjacent axons and dendritic

spines (Cali *et al.*, 2016). In brain regions with high neural activities, astrocytes have increased glycogen stores. By using ESG1A9 and IV58B6 to label glycogen in the mouse brain, distinct brain regions show different glycogen storage, with high levels in the hippocampus, striatum, the outer layer of the cortex, the cerebellar molecular layer, and the thalamic reticular nuclei, whereas glycogen levels are relatively low in the hypothalamus and most regions of the thalamus (Oe *et al.*, 2016).

It has been proposed that glycogen in astrocytes provides a critical source of glucose during periods of food deprivation and stress (Dienel, 2019). Glycogen phosphorylase is the rate-limiting enzyme in glycogen metabolism (Mathieu *et al.*, 2016). Lactate derived from astrocytic glycogen can be transported into neurons via MCT2 and can support the maintenance of ATP production in the brain (Matsui *et al.*, 2017).

Glycogen metabolism may also play roles in synaptic plasticity, learning, and memory (Alberini *et al.*, 2018; Cali *et al.*, 2016; Hackett *et al.*, 2016). Astrocytic glycogen mobilization is important for long-term memory formation, and blocking glycogen metabolism leads to memory impairment (Suzuki *et al.*, 2011). Hippocampal astrocyte to neuron lactate transport is mediated by MCT1 and MCT4. Glycogen breakdown is regulated by 3',5'-cyclic adenosine monophosphate (cAMP) and Ca^{2+}, and supports astrocytic potassium and glutamate uptake and glutamine synthesis. Disruption of glycogen metabolism in astrocytes may occur in epilepsy, AD, and type 2 diabetes (Bak *et al.*, 2018). Glycogen-derived energy is required for the elimination of glutamate and potassium ions from the synaptic gap. The blockage of glycogen metabolism increases the levels of synaptic extracellular potassium and glutamate, which can lead to hyperexcitability and can stimulate migraine headaches (Kilic *et al.*, 2018). In contrast, excessive accumulation of non-mobilizable glycogen can cause Lafora disease (Nitschke *et al.*, 2018).

2.3.4. Oligodendroglia—Four types of oligodendroglia have been identified based on morphology and are primarily distributed in the cerebral white matter (Perez-Cerda *et al.*, 2015). Single-cell analysis has further revealed divergent subpopulations of oligodendrocytes in the juvenile and adult mouse brain (Marques *et al.*, 2016; Zeisel *et al.*, 2015). Oligodendroglia are specialized glial cells that wrap axons with a multilamellar lipid structure called myelin and play pivotal roles in the functional maintenance and survival of neurons. In addition to their function in accelerating action potential propagation along the axon, oligodendrocytes are essential for energetic support to neurons (Philips and Rothstein, 2017). Oligodendrocytes have both a high rate of mitochondrial glucose metabolism and lactate production. These cells also have high PPP activities and use approximately 10–15% of glucose in the PPP compared with glycolysis (Amaral *et al.*, 2016a; Amaral *et al.*, 2016b). The energy metabolites produced by oligodendrocytes may contribute to lipid synthesis, trophic support to axons, and myelin protection (Amaral *et al.*, 2016b).

Oligodendrocytes transfer energy materials, such as pyruvate and lactate, to neurons through noncompacted regions of myelin and MCTs, which facilitate the fast delivery of energy metabolites to neurons for ATP synthesis (Fig. 4) (Philips and Rothstein, 2017). MCT1 in oligodendrocytes and MCT2 in neurons work together to transport lactate from oligodendrocytes to neurons, and downregulation of MCT1 results in axonal injury and

neuronal loss (Fig. 4) (Lee *et al.*, 2012; Morrison *et al.*, 2013). In the corpus callosum, neuron function is evaluated by detecting compound action potentials, and the absence of glucose abolishes these compound action potentials. Thus, MCT1 and GLUT1 are vital for providing the lactate and glucose derived from oligodendrocytes for axonal survival (Fig. 4) (Meyer *et al.*, 2018).

In addition to these transporters, gap junctions comprised of connexins (Cx) are also important for the intercellular delivery of ions, regulatory molecules, and metabolites, including glucose and lactate (Philips and Rothstein, 2017). Cx30 and Cx43 are located in astrocytes, and Cx32 and Cx47 are in oligodendrocytes. The coupling of Cx47-Cx43 and Cx32-Cx30 form channels for ionic and chemical delivery between oligodendroglia and astrocytes, respectively (Fasciani *et al.*, 2018; Orthmann-Murphy *et al.*, 2007). Some evidence suggests that gap junctions, including Cx30, Cx43, Cx32, and Cx47, contribute to energy metabolite transport from astrocytes to oligodendroglia (Morrison *et al.*, 2013; Nave and Werner, 2014). The metabolic interactions between neurons and oligodendrocytes serve to maintain neuronal function.

2.3.5. Microglia—Microglia account for 10–15% of cells in the brain where they play important roles in innate immune responses and neuroplasticity. Microglial densities are heterogeneous across brain regions, with the highest densities in the cortex, striatum, corpus callosum, hippocampus, SVZ, and rostral migratory stream (RMS), intermediate densities in the olfactory bulb, thalamus, hypothalamus, midbrain and brainstem, and the lowest density in the cerebellum (Fig. 5) (Stratoulias *et al.*, 2019; Tan *et al.*, 2020b; Yang *et al.*, 2013). The distinct subpopulations of microglia, defined by varying gene expressions, have unique functional characteristics (Stratoulias *et al.*, 2019). Most microglia express ionized calcium-binding adaptor molecule 1 (Iba1) and CD11b, although some $Iba1^{-}$/Chemokine (CCR) and fractalkine ($CX3CR1^{+}$) microglia are observed in the SVZ and the adjacent RMS, which terminates in the olfactory bulb. These $Iba1^{-}/CX3CR1^{+}$ microglia are involved in promoting neurogenesis (Fig. 5) (Stratoulias *et al.*, 2019). Microglia in the resting state is characterized by a ramified morphology. Upon stimulation, activated microglia change their morphology, with amplified soma and retraction of ramified processes (Yang *et al.*, 2013). The activated microglia have dynamic phenotypes, including the pro- or anti-inflammatory activities at different stages of disease, and it remains difficult to define the status of individual microglia (Colonna and Butovsky, 2017).

Glucose is the main energy source for microglial survival and function. Oxygen-glucose deprivation can lead to microglial death (Eyo *et al.*, 2013; Kacimi *et al.*, 2011). Multiple glucose transporters, including GLUT1, 3, 4, 5, 6, 8, 9, 10, 12, 13, and high hexokinase 2 (HK2) expression offer sufficient glucose influx for glial cells (Kalsbeek *et al.*, 2016; Wang *et al.*, 2019b). GLUT1 has the highest expression in microglia and predominately contributes to glucose uptake, particularly under inflammatory conditions (Wang *et al.*, 2019b). Microglia also use glutamine as an energy substrate, with high expression of glutamine receptors SLC1A5 and SLC38A1 (Liu *et al.*, 2018).

Microglial energy metabolism is dependent upon the degree of microglial reactivity. Quiescent microglia primarily rely on oxidative phosphorylation of glucose for energy

supply, while stimulated microglia transition from oxidative phosphorylation to glycolysis (Fig. 5) (Baik *et al.*, 2019). Despite less ATP generation in glycolysis than mitochondrial respiration, the rate of lactate production is faster than that of oxidative phosphorylation, which enables a rapid supply for energy-intensive processes such as proliferation, migration, and secretion (Cheng *et al.*, 2014; Peek *et al.*, 2017). AMP-activated protein kinase (AMPK), a sensor for AMP and ADP, inhibits mTOR phosphorylation and subsequently suppresses the expression of HIF-1α, the master transcriptional regulator of glycolysis (Cheng *et al.*, 2014). The inhibition of the mTOR pathway dramatically reduces the inflammatory responses of microglia. Thus, cellular metabolic pathways (mTOR-HIF-1α pathway) can alter the functional phenotypes of microglia (Baik *et al.*, 2019).

2.3.6 Cerebrovascular endothelial cells (CECs)—ECs have proliferative and migratory abilities after activation by a growth factor, such as vascular endothelial growth factor (VEGF). In recent years, EC metabolism and metabolic relationships with other cell types have played a pivotal role in health and diseases (Eelen *et al.*, 2018). Glycolysis, rather than oxidative phosphorylation, is the major glucose metabolism pathway for ATP production in these cells, which is beneficial for oxygen transfer to surrounding cells (Eelen *et al.*, 2018). Compared with ECs in other tissues, capillary ECs in the brain have more mitochondrial contents (Oldendorf *et al.*, 1977). When facing shear stress, oxidative phosphorylation in CECs becomes the major metabolic pathway, due to the increased expression of enzymes in the Krebs cycle and downregulated glycolytic genes (Cucullo *et al.*, 2011). A recent study about single-cell transcriptome atlas of murine ECs characterizes the ECs from multiple organs, and CECs have more expression of transporters of glucose (*Slc2a1*), amino acids (*Slc3a2*, *Slc7a5*), and fatty acids than ECs from other tissues (Kalucka *et al.*, 2020). The systems of tight junctions and material transportation in CECs are critical for maintaining the blood-brain barrier function, and glucose metabolism in CECs is involved in their modulation (Kalucka *et al.*, 2020; Zhang *et al.*, 2014). Low GLUT1 levels block angiogenesis and diminish the brain microvasculature network (Tang *et al.*, 2017). Patients with GLUT1 deficiency syndrome have low brain glucose levels and cerebral disorders with seizures, developmental delay, and motor disturbance (Wang *et al.*, 2005). The phosphatase and tensin homolog/protein kinase B (AKT) pathway in CECs increases monocarboxylic acid transporter 1 expression to promote lactate transport across the CECs, which is vital for maintaining lactate homeostasis contributing to hippocampal neurogenesis and cognitive function (Wang *et al.*, 2019a).

2.4. Signal modulation of glucose metabolism

Multiple signal molecules are involved in regulating brain glucose metabolism (Fig. 6). Wnt3a-mediated Wnt signaling activation enhances glucose metabolism by increasing HK activity and elevating glucose uptake and glycolytic rates in neurons, which is linked with the activation of the AKT and AMP-activated protein kinase (AMPK) pathways (Cisternas *et al.*, 2016; Cisternas *et al.*, 2019). Wnt3a ligand binding to the Frizzled receptor also inhibits glycogen synthase kinase-3β (GSK-3β) activity, and thereby activates AMPK, enhancing energetic effects (acetyl-coenzyme A carboxylase, 6-phos-phofructo-2-kinase) and mediating autophagy in hippocampal neurons (Mulukutla *et al.*, 2016; Ríos *et al.*, 2018). Additionally, Wnt signaling activation via Wnt5a stimulates nitric oxide-mediated glucose

metabolism in neurons. The canonical and non-canonical Wnt signals are all involved in the modulation of neuronal glucose metabolism (Cisternas and Inestrosa, 2017).

Peripheral insulin can enter the brain through the choroid plexus and cerebrospinal fluid, or directly via vascular endothelial cells (Duarte *et al.*, 2018). Moreover, the adult brain may also produce insulin via the gene *Insulin 2,* which exists in brain cells such as hippocampal neurons (Mehran *et al.*, 2012). Insulin is found in the hippocampus, cortex, anterior olfactory nucleus, cerebellar Purkinje neurons, amygdala, and other discrete nuclei, and insulin receptors are expressed in neurons and glial cells, indicating the role of insulin signaling in the regulation of brain function (Kleinridders *et al.*, 2014; Mehran *et al.*, 2012; Soto *et al.*, 2019). Insulin signaling in the hippocampus is important for maintaining spatial learning and memory, partly via the GLUT4-mediated glucose uptake (Pearson-Leary *et al.*, 2018; Soto *et al.*, 2019). Insulin signaling in the hypothalamic proopiomelanocortin astrocytes is involved in controlling cerebral glucose uptake (García-Cáceres *et al.*, 2016). Insulin binds to receptors in the brain and primarily modulates two signaling cascades, including the phosphoinositide 3-kinase (PI3K) pathway controlling metabolism and the mitogen-activated protein kinase pathway, regulating mitochondrial function, proliferation, and growth (Kullmann *et al.*, 2020). Enhanced insulin signaling can activate the PI3K-AKT pathway and stimulate glucose uptake by elevating the levels of GLUT3 and GLUT4 in the membrane (Gabbouj *et al.*, 2019; Liu *et al.*, 2015). In the mouse hippocampus, AKT1 and AKT3 are expressed in neurons, while AKT2 is primarily expressed in astrocytes, which may be implicated in insulin-dependent glucose metabolic regulation in neurons, microglia, and astrocytes (Gabbouj *et al.*, 2019; Levenga *et al.*, 2017).

2.5 Genetic factors influencing brain glucose metabolism

Genetic influences on brain glucose metabolism are vital for affecting brain function and neurological diseases. By comparing the brain glucose metabolism differences in elderly twins, it was discovered that the glucose metabolism in some brain regions, specifically the right and left parietal lobes and left temporal lobe, is affected more by genetics than by environment (Watanabe *et al.*, 2016). The genes modulating the expression of glucose metabolism enzymes and glucose transporters are the primary genetic factors affecting brain glucose metabolism. These key genes include pyruvate dehydrogenase kinase 3 and pyruvate dehydrogenase phosphatase catalytic subunit 1, which modulate glycolytic pathways, and GLUT1 deficiency syndrome, which causes a neurodevelopmental disorder (Goyal *et al.*, 2014; Tang *et al.*, 2019). Genome-wide association studies have further discovered many genes involved in regulating neuronal development and brain glucose metabolism, such as potassium ion channels, synaptic transmission and plasticity, neuropeptides and their receptors, and RNA-binding proteins, such as Fox-1 homolog 1. (Casanovas *et al.*, 2020; Goyal *et al.*, 2014; Kong *et al.*, 2018). In addition, the Dopamine D4 receptor gene with the 7-repeat (7R) allele may promote age-independent brain glucose metabolism in the cerebellum, inferior temporal cortex, and striatum, suggesting that carriers of the 7R allele have a stronger ability to resist age-induced brain glucose metabolism decline (Volkow *et al.*, 2013). Better understandings of the genetic factors affecting brain glucose metabolism are needed and may be beneficial for diagnosis and targeted treatment of brain diseases.

2.6 Glucose metabolism for non-energetic processes

2.6.1. Glucose metabolites for synthesis of biological compounds—In addition to carbon dioxide and ATP, glucose as the carbon and hydrogen carrier (C1–6) is involved in the synthesis of amino acids (C1–3 and H1, 2/6 for glutamine, alanine, glycine, and serine), lipid acids (C1,2 and H1,2,3/4,5,6), nucleotides (C1–5 and H2,4,5,6), NAPDH (H1/3), NADH (H4), glycogen, neurotransmitters, and neuromodulators (acetylcholine, glutamate, γ-aminobutyric acid, aspartate, and acetylcholine), glycolipids, and glycoproteins (Fig. 3) (Camandola and Mattson, 2017; Dienel, 2019), which has been verified by the tracking of carbon or hydrogen atoms transferred from glucose to other materials (Lane and Fan, 2015; Zhang *et al.*, 2019a). These products further support the cellular function and synthesis of biological macromolecules. Impaired glucose oxidation inhibits the production of glutamate, a key neurotransmitter, and causes altered neuronal network activity, highlighting the interaction of glucose metabolism and neuronal excitability (Jakkamsetti *et al.*, 2019).

2.6.2. Glycation—Glycation is a spontaneous, non-enzymatic reaction involving the attachment of sugar, such as glucose or glucose metabolites, to a protein or lipid and resulting in advanced glycation end-products (AGEs). N^{e}-(carboxymethyl)lysine, pyrraline, N^{e}-(carboxyethyl)lysine, methylglyoxal-lysine dimer, and glyoxal-lysine dimer are examples of frequently occurring AGEs (Kaur *et al.*, 2016). The glycating agent methylglyoxal (MGO) is generated from the decomposition of the glyceraldehyde 3-phosphate (GA3P) and dihydroxiacetone phosphate (DHAP) derived from glycolytic metabolites, and is catabolized by the glutathione (GSH)-dependent glyoxalase and NADPH-mediated aldose reductase systems (Fig. 7) (Vicente Miranda *et al.*, 2016). MGO can react with the cysteine, arginine, and lysine of proteins and can change the structural conformation, impairing protein function (Polykretis *et al.*, 2020). AGEs and the irreversible glycation process have been implicated in stroke and neurodegenerative diseases such as PD and AD (Ng *et al.*, 2019; Sharma *et al.*, 2019; Vicente Miranda *et al.*, 2016; Vicente Miranda *et al.*, 2017).

A recent study demonstrated that MGO can glycate superoxide dismutase 1 and increase cellular oxidative stress (Polykretis *et al.*, 2020), thus highlighting the important fact that glycation is not only involved in the aggregation of disease-related toxic proteins, but also influences cellular functions, such as antioxidative capacity. Aside from MGO, other glycating agents may play unknown roles in brain function and diseases. Aging and diabetes are currently considered the primary factors contributing to glycation and AGE generation, and studies suggest that enhancing the glyoxalase and aldose reductase systems and manipulating levels of NADPH and GSH are potential strategies for suppressing glycation-mediated neurotoxicity.

2.6.3. Non-metabolic functions of glycolytic enzymes and metabolites—In addition to maintaining energetic homeostasis, glucose metabolism molecules, such as intermediates and metabolic enzymes, also exhibit non-metabolic roles in regulating cellular activities, including the modification of proteins and DNA. Dysfunction in these non-metabolic processes has been implicated in disease processes such as malignancy and

immune responses (Ghosh-Choudhary *et al.*, 2020; Snaebjornsson and Schulze, 2018). For example, the pyruvate kinase isoform M2 activates signal transducer and activator of transcription 3 and focal adhesion kinase signals and plays a crucial role in decreasing stroke injury by enhancing neurogenesis (Chen *et al.*, 2018a).

HK2, a key glycolytic enzyme, plays a role in microglial-mediated neuroinflammation. In hypoxic conditions, HK2 is up-regulated, leading to the accumulation of acetyl coenzyme A (acetyl-CoA) and promoting transcription and expression of interleukin-1β. Blocking HK2 is protective against ischemic neurological injury (Li *et al.*, 2018). In addition, activation of AKT was shown to facilitate the binding of HK2 to the mitochondrial membrane, maintaining structural and functional integrity of mitochondria and reducing apoptosis (Li *et al.*, 2019).

Acetyl-CoA is implicated in histone acetylation and gene modification (Sivanand *et al.*, 2018). Acetyl-CoA synthetase 2, which generates acetyl-CoA, can act on chromatin and directly modulate histone acetylation in hippocampal neurons, which has been shown to subsequently regulate memory-related neuronal genes and affect long-term spatial memory in mice. This study demonstrated a connection between glucose metabolism, gene modulation, and neural function (Mews *et al.*, 2017). Inhibition of acetyl-CoA carboxylase 1 can increase the levels of acetyl-CoA in neurons and cause acetylation of histone H3K9, enhancing memory in the aging brain (Currais *et al.*, 2019) and making acetyl-CoA and its metabolic enzymes an interesting target involving molecular acetylation, memory, and aging.

Glycolytic enzymes have also been implicated in neurotransmission. Glutamate neurotransmission in astrocytes can be modulated by the binding of serine racemase to the glycolytic enzyme glyceradehyde-3-phosphate dehydrogenase (GAPDH), which decreases the amount of available D-serine for N-Methyl-D-aspartic acid (NMDA) receptor activation (Suzuki *et al.*, 2015). GAPDH can also translocate into the nucleus and interact with poly (ADP-ribose) polymerase-1, causing overactivation in settings of oxidative stress and exacerbating stroke injury (Nakajima *et al.*, 2015). GAPDH nuclear translocation, aggregation, and binding to toxic proteins, such as β-amyloid peptides, tau protein, and α-synuclein, have been linked to neuronal death in neurodegenerative diseases such as AD and PD (Gerszon and Rodacka, 2018). Further, nitric oxide-mediated GADPH nitrosylation has been shown to promote Rheb degradation and decreases mTOR activation. Inhibition of this GAPDH nitrosylation exerted antidepressant effects (Harraz *et al.*, 2016).

Enolase 2 (ENO2), also known as γ-enolase or neuron-specific enolase, is a glycolytic enzyme located in neuronal cytosol and synaptic plasma membranes. Blocking this enzyme with an anti-ENO2 antibody was shown to promote the production of hydrogen peroxide and cause brain cell death via a non-apoptotic pathway (Yamamoto *et al.*, 2015), suggesting a neuroprotective effect of ENO2. Additionally, the role of ENO2 in the PI3K/AKT and MAPK/ERK pathways has been shown to activate inflammation, influencing cell survival, and has been shown to have neurotrophic functions, such as neurite regeneration (Hafner *et al.*, 2012; Haque *et al.*, 2018; Haque *et al.*, 2016).

Understanding the non-metabolic functions of glucose metabolites and enzymes is critical to fully comprehend the networks between glucose metabolism and neuronal function and may allow for targeted modulation of metabolism, neurotransmission, cellular survival, and neuronal functions.

3. Methods for evaluating brain glucose metabolism

3.1. Positron emission tomography (PET)

Fluorodeoxyglucose F18 (^{18}F-FDG) is transported into brain tissue by GLUTs and is phosphorylated ^{18}F-FDG-6-phosphate by HK. Because FDG is not further metabolized, it is then trapped in cells and can be measured for evaluating brain glucose uptake (Fig. 2B) (Izuishi *et al.*, 2014). Thus, FDG-PET directly reflects cerebral glucose uptake, but not glucose metabolism. Several parameters impacting FDG transport between blood and brain may lead to changes in glucose uptake under pathological conditions (Backes *et al.*, 2011; Walberer *et al.*, 2012; Wang *et al.*, 2020).

Advancements in PET imaging have led to the development of new PET probes, which can be combined for studying the correlation of glucose metabolism and other factors in disease, such as (^{18}F) 2-tert-butyl-4-chloro-5–2H-pyridazin-3-one (mitochondrial labeling) and FDG-PET, ^{123}Ioflupane brain single-photon emission computed tomography (dopamine transporter) and FDG-PET, and fluorine-18-l-dihydroxyphenylalanine-PET (reflecting the dopamine distribution) and FDG-PET (Huber *et al.*, 2020; Ruppert *et al.*, 2020; Terada *et al.*, 2020).

3.2. Magnetic resonance spectroscopy (MRS)

Radioactive isotopes to track metabolism are widely used for studying metabolic pathways and rates of transport within the brain, including oxygen consumption (^{17}O, ^{13}C, ^{1}H), glucose consumption (^{13}C, ^{1}H, ^{19}F), creatine kinase/ATPase flux (^{31}P), neurotransmitter flux (^{13}C, ^{1}H), and pH (^{1}H) (Hwang *et al.*, 2019; Hyder and Rothman, 2017). The application of specific radioisotopes can trace the fate of single or multiple atoms of the glucose structure and metabolites. For example, glycogen can be detected with the specific C1 glycogen peak after the movement of the ^{13}C from glucose to glycogen (DiNuzzo, 2013). Intravenous administration of ^{13}C-labelled nutrients indicates the turnover flux of lactate is the highest of all metabolites and contributes to the Krebs cycle intermediates (Hui *et al.*, 2017). Recently, ^{1}H-MRS has been demonstrated as a powerful tool monitor the metabolism of ^{13}C-enriched substrates in brain (Dehghani *et al.*, 2020).

3.3. Microdialysis

Microdialysis is an invasive measure of glucose metabolism from directly within the brain. A cannula is implanted into the target region of the brain, and a microdialysis probe is then inserted through the cannula to collect samples of metabolic substrates from the interstitial fluid among brain cells via perfusion of artificial cerebrospinal fluid, allowing for the detection of real-time changes in small molecules in the brain interstitium (Le Douce *et al.*, 2020). The collected samples are separated by high-performance liquid chromatography and determined with mass spectrometry, biochemical reactions,

immunoassays (radioimmunoassay and enzyme linked immunosorbent assay), microchip electrophoresis, and microfabricated fluidic systems (Davies *et al.*, 2000; Sandlin *et al.*, 2005; Saylor and Lunte, 2018). The enzyme-based microelectrodes can be used for real-time measurements of cerebral interstitial fluid (Barros *et al.*, 2018a), but this technology has low spatial and temporal resolution and may cause local brain disruption. Currently, microdialysis is widely used to detect the levels of glucose, lactate, pyruvate, and insulin in the brain to investigate the role of cerebral metabolism in brain function and disease. Some studies indicate that lactate in the hippocampal interstitial fluid supports memory function (Harris *et al.*, 2016). Conversely, increased glucose or lactate levels in the hippocampal interstitial fluid were related with elevated amyloid-beta or tau levels, which may contribute to the formation of amyloid plaques and neurofibrillary tangles (Harris *et al.*, 2016; Holth *et al.*, 2019; Macauley *et al.*, 2015; Roh *et al.*, 2012; Stanley *et al.*, 2016). Larger molecules, such as proteins, cytokines, neuropeptides, and monoclonal antibodies, can also be analyzed via microdialysis (Jadhav *et al.*, 2016; Perkins *et al.*, 2021).

High-resolution electrochemical biosensors may be used as an alternative method to detect glucose, lactate, and glutamate levels within the brain (Naylor *et al.*, 2012), making microdialysis a promising and valuable technique for metabolomics studies (Hammarlund-Udenaes, 2017). Limitations of microdialysis include localized tissue injury caused by the inserted probes (200–500 μm in external diameter), difficulty with precise targeting of small target nuclei, localized sampling that may not represent the brain as a whole, and levels of intracellular metabolites below the limits of detection. Utilizing specialized perfusion fluid, such as dexamethasone, an anti-inflammatory drug, may decrease local lesion burden without marked effects on dopamine terminals, tyrosine hydroxylase, or the dopamine transporter after probe implantation in the striatum of rats (Jaquins-Gerstl and Michael, 2020; Nesbitt *et al.*, 2015).

3.4. Imaging methods for metabolic detection

3.4.1. Spectroscopic imaging—Fourier transform infrared (FTIR) spectroscopy can detect biochemical materials, including nucleic acids, proteins, lipids, and carbohydrates within cells, tissues, and even extracellular vesicles. The unique spectrum of the materials is based on the wavelength and quantity of infrared radiation (Su and Lee, 2020). FTIR imaging can simultaneously detect the changes of lipid and protein contents, such as Aβ protein and Lewy bodies, in the brain (Ali et al., 2018; Araki et al., 2015). The glycogen and lactate in the frozen slice of the brain can be detected by FTIR spectroscopic imaging based on the intensity at 1152 and 1125 cm^{-1} respectively (Hackett *et al.*, 2016). This approach can be used to study spatiotemporal alterations of metabolites in the brain.

Deuterium-labeled glucose given to cells or animals can be used for tracking the carbon–deuterium bonds in macromolecules with multichannel stimulated Raman scattering microscopy. The specific Raman peaks of carbon-deuterium bonds can distinguish various types of glucose-derived macromolecules (Shen *et al.*, 2019b). This microscopy technique can elucidate the metabolic fate of glucose in diverging biosynthesis pathways, which may be superior to other glucose-imaging tools, such as PET and fluorescence, which are

primarily used for visualizing the earlier processes of glucose metabolism (Zhang *et al.*, 2019a).

3.4.2. Autoradiography—Quantitative autoradiography can achieve a high degree of spatial localization of target materials via the radioactive element, which is useful in evaluating cerebral blood flow, glucose metabolism, and protein changes (Saré *et al.*, 2019; Schmidt and Smith, 2005). 2-Deoxy-D-glucose (2DG) is an analogue of glucose and is used for the measurement of the rates of glucose metabolism *in vivo*. After intravenous injection of [^{14}C]-2DG in animals, brain sections were exposed to autoradiographic film for several days. The autoradiographic images provided a quantitative metabolic map of the brain (Le Douce *et al.*, 2020; Lundgaard *et al.*, 2015). ^{18}F-FDG can also be used for autoradiographic images to assess the glucose uptake levels in different brain areas (Putzu *et al.*, 2018). Therefore, autoradiography presents a method for measuring regional rates of metabolites and understanding glucose metabolism-based brain actions and diseases.

3.4.3. Mass spectrometry imaging—Mass spectrometry imaging can provide more information about glucose metabolic fate than PET imaging (Kleinridders *et al.*, 2018). Mass spectrometry imaging enables imaging of the spatial distribution of multiple molecules such as metabolites, glycans, peptides, and lipids without labeling. This is achieved by detecting the mass-to-charge value of the ionized molecules on the surface of the sample with a mass spectrometer and mapping a construction of the values distributed on the sample's surface using computational software (Buchberger *et al.*, 2018; Luan *et al.*, 2019). Matrix-assisted laser desorption/ionization, desorption electrospray ionization, and nanostructure-initiator techniques are used for the qualitative analysis of metabolites (Luan *et al.*, 2019). This chemical analysis tool can visualize the spatial distributions of glucose metabolites and characterize region-specific metabolism in the brain. It is also a powerful tool for researching the metabolic crosstalk between the various brain regions. However, without the chromatographic assistant, mass spectrometry imaging is limited in its analytical depth. The use of a laser capture microdissection system coupled with liquid chromatography mass spectrometry (LC-MS) can enhance the analysis of regions of interest for further molecular identification (Dewez *et al.*, 2020; Dilillo *et al.*, 2017).

3.4.4. Biological imaging—Metabolic imaging based on the histochemistry of metabolic enzymes, such as glucose-6-phosphate dehydrogenase (G6PD), LDH, and GAPDH, is a powerful tool for investigating metabolic configurations, specifically allowing for the metabolic characterization of individual cells within the tissues (Miller *et al.*, 2017). According to the catalytic activity of metabolic enzymes at key nodes of glucose metabolism (Fig. 3), other biological functions of these enzymes, such as the redox balance and cell signaling events, can be determined via the enzyme-dependent metabolic imaging method. NADH autofluorescence has a short lifetime of ~400 ps by two-photon excitation. Upon enzymatic binding to NADH, this fluorescence lifetime extends to 2000 ps. Thus, the lifetime of NADH can be used to evaluate the ratio of glycolysis to mitochondrial oxidative phosphorylation (Bernier *et al.*, 2020). Biosensors are sensitive and selective detectors that can be used for observing and quantifying specific biomolecules. Förster resonance energy transfer-based biosensors are exploited for the detection of DNA, miRNA, proteins, and

enzymes (Wu *et al.*, 2020; Zhang *et al.*, 2019b). A C1-type d-glucose-conjugated fluorescent probe has competitive uptake capacity for glucose and is employed for glucose uptake imaging (Cheng *et al.*, 2020b). Some genetically encoded metabolite sensors, including the iGlucoSnFR-TS (glucose sensor), Frex family (NADH sensors), LigA-cpVenus (NAD^+ sensor), Peredox, RexYFP, SoNar (NAD^+/NADH ratio sensors), iNap family (NADPH sensors), and Apollo-$NADP^+$ ($NADP^+$ sensor), are used for the detection of cerebral glucose metabolism (Díaz-García *et al.*, 2019; Zhang *et al.*, 2018b). These metabolic enzymes and biosensor-enabled imaging methods can advance the understanding of the features and functions of glucose metabolism in the brain.

3.5. Metabolomics assays

Metabolomics can provide systematic information on metabolites and their crosstalk in brain function and disease (Luan *et al.*, 2019). Hundreds of metabolites in brain tissue or cerebrospinal fluid can be detected with nuclear magnetic resonance (NMR), gas chromatography-mass spectrometry (GC-MS), LC-MS, ion mobility systems, and capillary electrophoresis (An *et al.*, 2018; Wishart, 2019). GC-MS can detect volatile and non-polar compounds, as well as some polar metabolites (neurotransmitters, polyunsaturated fatty acids, amines, and amino acids), while polar chemicals, non-volatile, or thermo-unstable compounds can be determined by LC-MS (Luan *et al.*, 2019). Compared with MS, NMR is less sensitive to chemicals, but retains chemical integrity without chromatographic separation or ionization and identifies compounds with hydrogen chemical shift fingerprints (Wishart, 2019). Additionally, mass spectrometry imaging techniques can be used to select areas of interest in tissue samples for metabolomics analysis, which provides the spatial distributions of metabolites (Johnson *et al.*, 2016). Metabolomics is suitable for understanding the chemical composition of the brain and unveiling metabolic signals (Gonzalez-Riano *et al.*, 2016). With further development of MS sensitivity, coverage, speed, and single-cell technique, the high-throughput of metabolomics enables large scale metabolome profiling, real-time determination, and spatial resolution (single cell, organelle, and intracellular and extracellular metabolites) (Zampieri *et al.*, 2017). Challenges still exist in the validation of metabolites, biological interpretation of novel metabolites, and comprehensive informatics for metabolomic analyses (Cui *et al.*, 2018; Johnson *et al.*, 2016). Currently, many metabolomics libraries (such as AMDIS, MASCOT, XCMS) and metabolite identification databases serve for data analysis (Kusonmano *et al.*, 2016). The Human Metabolome Database (www.hmdb.ca) and MetaboAnalyst (http://metaboanalyst.ca) are updated and provide comprehensive information about the biological function of metabolites, metabolic pathways and their integration with other omics data (Chong *et al.*, 2018; Wishart *et al.*, 2018). New informatics strategies, such as the metabolic reaction network-based recursive algorithm, are major drivers in overcoming some of the challenges presented with metabolomic analysis (Domingo-Almenara *et al.*, 2019; Shen *et al.*, 2019a). The integration of metabolomics, together with the other omics, including genomics, transcriptomics, and proteomics, will be promising for gaining new insights into the mechanisms underlying neurological disorders and finding novel methods for diagnosis and evaluation of therapeutic efficacy in disease.

3.6 Metabolic endpoint measurements

Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) are important parameters reflecting glycolysis levels. Normally, cells have low ECAR and high OCR due to the advantage of oxidative phosphorylation. The addition of glucose, as a new substrate, causes an elevation of ECAR and decrease of OCR, reflecting a shift away from oxidative phosphorylation and toward glycolysis. Mitochondrial inhibition with oligomycin (ATP synthase inhibitor) and rotenone (mitochondrial electron transport chain blocker by inhibiting complex I) increases ECAR and decreases OCR (Klinge, 2020; Mookerjee et al., 2017). Mitochondrial phosphate/oxygen ratios indicate the generated ATP per oxygen atom consumption, and suggest the oxidation of pyruvate plus malate (2.73), oxidation of succinate (1.64), and complete oxidation of glucose (2.79) (Hinkle, 2005; Mookerjee *et al.*, 2017). Many materials, such as ATP, ADP, oxygen, multiple ions, and metabolic substrates can be quantified and subsequently employed to evaluate the metabolic status, though it remains challenging to precisely understand complex metabolic networks and modulation with the current metabolic parameters.

4 Glucose metabolism in aging brain

Aging is a common risk factor for many neurological diseases. Multiple changes in glucose metabolism-related factors, such as glucose transport, mitochondrial function, DNA repair, and neurotrophic factors, contribute to aging in the brain (Camandola and Mattson, 2017). Aging neurons primarily rely on glucose oxidation via glycolysis, rather than astrocytic lactate support, as an energy source, and the enzymes of glycogen metabolism increase with aging in both astrocytes and neurons (Drulis-Fajdasz *et al.*, 2018). However, the ability of neurons to use ketone bodies as an energy source may be maintained even when glucose availability is reduced (Courchesne-Loyer *et al.*, 2017). Brain glucose uptake declines with normal aging in a greater proportion to oxygen consumption, which leads to a reduction in aerobic glycolysis that is most obvious in brain areas that utilize more aerobic glycolysis in youth (Goyal *et al.*, 2017). Electron microscopy has demonstrated that myelinated fibers in the aging mouse brain have longer and thicker mitochondria, which was associated with lower ATP levels and increased production of reactive oxygen species (ROS) (Stahon *et al.*, 2016). Aging-related metabolic alterations in the fly *Drosophila melanogaster* brain were recently characterized by single-cell transcriptome sequencing, which revealed changes in cell composition (a relative increase of glia), more prominent aging in glia versus neurons, decreased mitochondrial turnover, a decline in oxidative phosphorylation levels, and unique changes of ribosomal gene expression (Davie *et al.*, 2018). Ultimately, dysfunction of glucose metabolism related to aging may be vital for the occurrence and progression of neurological diseases.

5 Glucose metabolism in neurologic diseases

Glucose metabolism plays a central role in maintaining brain cell viability and function and is also involved in the progress of multiple neurological diseases (Table 1). Chemical manipulation of the glucose metabolism pathway is promising for the development of new drugs to treat these diseases. Chemicals regulating glucose transportation or metabolism

(Table 2) may become tools for experimental research and have the potential for clinical application.

5.1. Ischemic brain injury

5.1.1. Glucose metabolism changes in ischemic brain—Synaptic dysfunction is the earliest consequence of cerebral ischemia and may occur within seconds, resulting from aberrant transmitter release at the synapse, dysfunction of ATP-dependent sodium and calcium ion-motive ATPases, and calcium ion accumulation within synaptic terminals (Hofmeijer and van Putten, 2012). In focal ischemic stroke, neurons in the ischemic core die rapidly by necrosis, and more distant neurons may undergo delayed death by apoptosis. Thus, brain areas rich with neurons and high in metabolic activity suffer most from ischemic injury (Schaafsma *et al.*, 2003). Cellular glucose deprivation is an important pathological mechanism of ischemic brain lesions.

After cardiac arrest (CA) exposure, brain glucose metabolism decreased in the cortex at 2, 4, 24, 48 h, and even 5 weeks after the return of spontaneous circulation (ROSC), and HK I and II levels reduced in injured brain areas (Hahn *et al.*, 2014; Li *et al.*, 2015; Putzu *et al.*, 2018), suggesting the decreased capacity of brain glucose metabolism in injured neural cells. PET scan at 3h post-ROSC indicated that a high forebrain-to-hindbrain ratio of ^{18}F-FDG uptake predicted good neurological outcomes after CA (Kim *et al.*, 2019). In a rat model of stroke, FDG uptake is reduced in the infarct area, while it is elevated in the peri-ischemic region 2h after reperfusion (Walberer *et al.*, 2012; Yuan *et al.*, 2013). The cells in the peri-ischemic region may use aerobic glycolysis to support energy needs in hypoxic conditions (Yuan *et al.*, 2013).

Multiple factors, such as cerebral blood flow and oxygen availability, can influence brain glucose metabolism. After CA, the blood flow and oxygen metabolism in the whole brain are reduced during the first week after ROSC, most prominently in the occipital cortex, putamen, and white matter (Hahn *et al.*, 2014). Oxygen remains critical for brain glucose metabolism in the glycolytic pathway, and it has been demonstrated that reperfusion with hyperoxia (pressure of arterial oxygen ≥ 300 mmHg) after CA is associated with poor functional outcomes (Richards *et al.*, 2007; Roberts *et al.*, 2018). Additionally, hypothermia exerts neuroprotection in ischemic brain injury (He *et al.*, 2019; Zhen *et al.*, 2013) by preserving the ATP levels and decreasing the glucose metabolism flux into lactate (Erecinska *et al.*, 2003).

Our understanding of the relationship between brain glucose uptake and metabolism changes with post-ischemia or post-stroke outcomes remains limited, and these changes and outcomes are further influenced by complex factors such as age, brain region, and time from injury.

5.1.2. Glucose metabolism in glial cells after brain ischemia—Microglia have a stronger capacity for energy production via non-oxidative glucose metabolism compared to neurons and astrocytes, improving their survival in peri-infarct areas (Backes *et al.*, 2016). However, hyperglycolysis within the penumbra after brain ischemia has been shown to exacerbate brain injury by activating microglia and promoting ROS production. Inhibiting

HK2, a key glycolytic enzyme, can suppress microglial activation and decrease ischemic brain injury (Li *et al.*, 2018). It has also been shown that fractalkine receptor chemokine (C-X3-C motif) ligand 1 (CX3CL1) signaling in microglia, which modulates metabolism by increasing oxidative phosphorylation and reducing glycolysis after CA, supports the expression of anti-inflammatory genes and results in reduced brain injury (Lauro *et al.*, 2019). In the early recovery after oxygen-glucose deprivation exposure, the increased glucose mobilization via the PPP and tricarboxylic acid cycle in surviving astrocytes contributes to energetic support and recovery (Amaral *et al.*, 2010). Brain ischemia also triggers MCT1 expression in oligodendrocytes, particularly in the peri-infarct striatum, which may allow for lactate transportation from astrocytes to produce sufficient energy (Zhou *et al.*, 2018a).

5.1.3. CECs in brain ischemia—CECs are highly associated with stroke injury and treatment. Targeting tight junctions or transporters in CECs is promising for regulating endothelial homeostasis and function in stroke (Abdullahi *et al.*, 2018). Decreasing the loss of tight junction proteins in stroke can alleviate brain lesion size via inhibition of autophagy (Kim *et al.*, 2020; Zhang *et al.*, 2018a). miR-34a can reduce the mitochondrial oxidative phosphorylation, ATP production, and cytochrome c levels in CECs, which contribute to the destruction of the blood-brain barrier (Bukeirat *et al.*, 2016). Knockout of miR-34a can markedly decrease the permeability of the blood-brain barrier and improve stroke outcomes (Hu *et al.*, 2020). Targeting some miRNAs, such as miR-34a, miR-15a miR-26b, and miR-212/132, has the potential to reduce ischemic brain injury associated with stroke by modulating CECs (Burek *et al.*, 2019; Ren *et al.*, 2019; Shen and Ma, 2020). miR-126 derived from the exosomes of CECs has neurorestorative effects in stroke mice (Venkat *et al.*, 2019). Transcriptional profiles of CECs in stroke provide more information for understanding the role of CECs in ischemia and may suggest some novel targets for modulating CECs for stroke treatment (Munji *et al.*, 2019).

5.1.4. Glucose metabolism modulation for decreasing ischemic brain injury —Glucose metabolism regulation is a promising strategy in defense against ischemic injury. NADPH, a metabolic byproduct of PPP, has antioxidant abilities and reduces intracellular oxidative stress. Intravenous administration of NAD^+ and NADPH has demonstrated neuroprotective effects in ischemic stroke (Huang *et al.*, 2018; Li *et al.*, 2016). Increasing the PPP flux by ischemic preconditioning, enhancing G6PD activity, increasing TP53-induced glycolysis and apoptosis regulator (TIGAR) expression, PFKFB3 inhibition, or suppressing oxygen-sensing prolyl hydroxylase domain proteins can decrease neuronal apoptosis and protect against ischemic brain injury (Burmistrova *et al.*, 2019; Cao *et al.*, 2017; Li *et al.*, 2014; Quaegebeur *et al.*, 2016). However, NADPH also mediates the ROS generation caused by NADPH oxidase (NOX). Thus, the cooperation of NOX inhibition and NADPH may better alleviate ischemic brain damage (Qin *et al.*, 2017).

The glutathione glycosylase system (GSH) is responsible for MGO elimination. Inhibition of the GSH results in MGO accumulation, leading to increased glycation, including occludin glycation, which was shown to increase blood-brain barrier permeability, increase oxidative stress, and exacerbate the post-stroke injury (Wang *et al.*, 2016b). It has been demonstrated

that N-acetylcysteine (NAC) can decrease glycation-mediated stroke risk by enhancing the GSH-dependent MGO elimination (Wang *et al.*, 2018). Activation of glutamate oxaloacetate transaminase by protein kinase C epsilon or isoflavone reduces ischemic stroke lesions by metabolizing neurotoxic glutamate and promoting the tricarboxylic acid cycle (Khanna *et al.*, 2017; Rink *et al.*, 2017; Xu *et al.*, 2020). Resveratrol, a known activator of sirtuin 1, stimulates the glycolytic rate and enhances ischemic tolerance and neuroprotection in the ischemic penumbra (Koronowski *et al.*, 2017). The inhibition of the abnormal astrocytic connexin-43 opening with carbenoxolone (Table 2) has neuroprotective effects in cerebral ischemia/reperfusion injury as well (Yin *et al.*, 2018). TIGAR-mediated metabolic modulation in astrocytes suppresses the inflammatory injury to neurons after ischemia/reperfusion (Chen *et al.*, 2018b). Targeting the cerebral glucose metabolism is promising for neuroprotection in ischemic brain injury.

5.2. Alzheimer's disease

5.2.1. Hypometabolism in AD brain—In AD patients with cognitive decline, the accumulated amyloid-β (Aβ) peptide and hyperphosphorylated tau proteins in the brain contribute to dysfunction and loss of synapses and neuronal death. FDG-PET studies have consistently demonstrated reduced cerebral glucose utilization in AD which are correlated with Aβ and tau pathologies. Aβ aggregates induce oxidative stress, which impairs the enzymes involved in glucose metabolism and decreases glucose utilization for ATP biosynthesis (Butterfield and Halliwell, 2019; Gordon *et al.*, 2018). In the brain of female AD mice, glucose-6-phosphate is accumulated and thereby inhibits hexokinase activity in glycolysis and the PPP. Cortical synaptic mitochondrial complex I function is reduced, causing glucose hypometabolism, energy failure, and neuronal death (Demarest *et al.*, 2020).

Disturbance of glucose transport occurs in AD, with decreased levels of GLUT1 and GLUT3, particularly in the cerebral cortex (Szablewski, 2017; Winkler *et al.*, 2015). Low glycolytic rates in the AD brain lead to higher glucose levels, which can down-regulate GLUT3 (An *et al.*, 2018). In a *Drosophila* model of adult-onset AD, genetic overexpression of glucose transporters in neurons or stimulation of glucose uptake by metformin increased survival of the flys (Niccoli *et al.*, 2016). These findings suggest that dysfunction of glycolytic enzymes and glucose transport contribute to hypometabolism in regions of Aβ aggregation and may be linked to phenotype severity.

5.2.2. Dysfunction of glucose metabolism in AD—It has been proposed that multiple pathogenic factors, including genetic mutation, aging, and environmental toxins, impair glucose metabolism and contribute to neuronal degeneration in AD patients (Fig. 7). This hypothesis has been supported with evidence such as altered thiamine metabolism and cerebral insulin resistance in AD patients (Chen and Zhong, 2013). Inhibition of insulin-mediated brain PI3K/AKT pathway may block tau dephosphorylation and exacerbate neuronal degeneration (Duarte *et al.*, 2018; Kleinridders *et al.*, 2014). The ε4 allele of apolipoprotein E (APOE4) is a predominant genetic risk factor for AD, which affects brain insulin signaling and glucose and amyloid metabolism by inducing deficits in glycolysis, glucose uptake, and mitochondrial respiration (Emrani *et al.*, 2020; Keeney *et al.*, 2015;

Wu *et al.*, 2018). In AD patients with APOE4, more tau accumulation and brain atrophy are observed in the medial temporal lobe, causing memory impairment (Emrani *et al.*, 2020). Dysfunction of glucose metabolism has been observed in the early phase of AD. Embryonic neurons derived from the 3xTg-AD mouse hippocampus have significant mitochondrial respiration reduction (Yao *et al.*, 2009). Glucose uptake in the amygdala, entorhinal cortex, and hippocampus is decreased in the early stage of 3xTg-AD female mice (6- to 7-month old) without senile plaque formation, and this has been linked to impaired synthesis of L-serine and D-serine. L-serine is produced from the glycolytic intermediate 3-phosphoglycerate and is the precursor of D-serine, which is involved in regulating synaptic plasticity (Le Douce *et al.*, 2020).

Mitochondrial dysfunction, reflected by reduced [^{18}F]BCPP-EF uptake, has been found in the parahippocampus and may precede glycolysis-related hypometabolism in the early stages of AD (Terada *et al.*, 2020). Cerebral β-amyloidosis leads to an increase in Ca^{2+} levels in synapses and mitochondria and has been linked to plaque deposition and neuronal death (Calvo-Rodriguez *et al.*, 2020). Pentatricopeptide repeat-containing protein 1 (PTCD1) in mitochondria is required for ATP production via oxidative phosphorylation. Gene *PTCD1* variant is found in AD patients and disrupts neuronal energy homeostasis, suggesting that the AD-related gene alteration may cause dysfunction of glucose metabolism and further contribute to impaired synaptic plasticity and behavioral deficits in the early phases of AD (Fleck *et al.*, 2019).

Metabolic intermediate deficiencies have also been associated with cognitive impairment in AD. O-linked N-acetylglucosamine (O-GlcNAc) is produced via the glucose metabolism pathway, and aging has shown a decline of this metabolite in the hippocampus of mice ages 18–22 months (Wheatley *et al.*, 2019). O-GlcNAc deficiency was shown to promote the production of hyperphosphorylated tau and amyloidogenic Aβ-peptides, resulting in memory impairment in mice (Pinho *et al.*, 2018; Wang *et al.*, 2016a). Increasing O-GlcNAc levels in the hippocampus can enhance fear memory development in young adult mice and rescue the impairments of spatial learning and memory in aging mice (Wheatley *et al.*, 2019). Increased lactate levels in the hippocampal interstitial fluid are related to memory decline in AD mice (Harris *et al.*, 2016). Additionally, the elevation of plasma, but not cerebrospinal fluid, lactate levels are highly associated with Aβ aggregation (Kavanagh *et al.*, 2019). More studies are required to clarify whether disturbances of specific steps in glucose metabolism are directly related to etiologies and the natural history of AD in the absence of this gene mutation.

5.2.3. Dysfunction of microglial glucose metabolism in AD—Dysfunction of glucose metabolism in microglia may occur in AD. The metabolism of microglia is shifted from oxidative phosphorylation to aerobic glycolysis during Aβ-induced inflammatory activation, boosting microglial glycolysis, increasing interferon-γ and Aβ phagocytosis (Baik *et al.*, 2019). Rutin, a natural flavonoid in many foods, can promote the microglial metabolic transition from anaerobic glycolysis to oxidative phosphorylation, enhancing ATP production and Aβ phagocytosis (Pan *et al.*, 2019). Thus, maintaining oxidative phosphorylation in microglia has the potential for improving brain injury in AD. A variant of the microglial surface receptor triggering receptor expressed on myeloid cells

2 (TREM2), has been identified in AD patients and is linked to disruption of energy metabolism through mTOR signaling (Ulland *et al.*, 2017), further suggesting that abnormal metabolism in microglia occurs in AD and modulation of microglial metabolism may be a potential therapeutic strategy.

5.2.4. Targeting impaired glucose metabolism for AD therapy—Peripheral metabolism disorders, such as glucose intolerance, have been correlated with AD progression (Griffith *et al.*, 2019). Insulin resistance is a risk factor for age-related cognitive impairment and AD. Accordingly, interventions that enhance insulin sensitivity such as regular exercise and intermittent fasting may reduce the risk of AD (de Cabo and Mattson, 2019; Mattson, 2012). Drugs that enhance insulin sensitivity also have the potential to be beneficial for patients with mild cognitive impairment and AD, although this remains to be established. Administration of metformin reverses Aβ-induced metabolic defects and decreases protein aggregation in neurons (Teo *et al.*, 2019). Another approach is to circumvent an impairment in neuronal glucose utilization by either modifying food intake so as to include regular periods in a ketogenic state with either intermittent fasting or ketogenic diets (Cunnane *et al.*, 2020). Alternatively, supplementing the diet with a ketone ester has proven effective in lessening Aβ and tau pathologies and improving cognitive function in mouse models of AD (Cheng *et al.*, 2020a; Kashiwaya *et al.*, 2013). Mitochondrial metabolic remodeling has emerged as an area of focus for potential AD diagnosis and treatment (Peng *et al.*, 2020; Teo *et al.*, 2019). Increasing glucose uptake via chemicals, such as metformin, has been shown to improve AD symptoms (Niccoli *et al.*, 2016). Activating Wnt signaling by andrographolide or lithium ions can enhance glucose metabolism in cortical and hippocampal neurons and delay the neuropathological progression in AD mice (Fig. 6) (Cisternas *et al.*, 2019). L-serine and cilostazol have been shown to improve cognitive function in AD patients and mice by regulating glucose metabolism and enhancing glucose utilization (Le Douce *et al.*, 2020; Lee *et al.*, 2019). A deeper understanding of the links between glucose metabolism and AD remains critical for advancements in diagnosis, prevention, and therapies.

5.3. Parkinson's disease

5.3.1. Hypometabolism in PD brain—Intraneuronal accumulation of the misfolded protein a-synuclein is a classic feature of PD pathology. The dysfunction and death of dopaminergic neurons in the substantia nigra pars compacta inhibit dopaminergic input to the striatum, causing motor dysfunction with bradykinesia, rigidity, and resting tremor, and nonmotor symptoms, including cognitive, sleep, mood, and olfactory dysfunction (Kalia and Lang, 2015). In newly diagnosed PD patients, reduced FDG in the parietal cortex is associated with cognitive decline (Firbank *et al.*, 2017). Hypometabolism in the caudate nucleus and inferior parietal lobule has been associated with PD (Meles *et al.*, 2017). Dopamine depletion in the putamen is followed by reduced ^{18}F-FDG uptake in PD patients (Ruppert *et al.*, 2020). Ultimately, hypometabolism in multiple brain regions occurs as the disease progresses.

5.3.2. Mutant genes in PD impair mitochondria metabolism—Gene mutations of *PARK6* (PINK1), *PARK2* (parkin), and *PARK7* (DJ-1), are linked to familial PD and the

proteins encoded by these genes are each important for mitochondrial homeostasis. Parkin can regulate glucose metabolism via the ubiquitination of pyruvate kinase 2, decreasing enzymatic activity (Liu *et al.*, 2016). Knockout of the *PARK2* gene impairs glycolysis in neurons (Bogetofte *et al.*, 2019). These links suggest that mitochondrial metabolic impairment caused by these gene mutations may mediate neuronal degeneration in PD (Knight *et al.*, 2014).

5.3.3. Modulation of glucose metabolism for PD treatment—A recent clinical trial showed that the glucagon-like 1 peptide analog exenatide improves motor function in patients with PD (Athauda *et al.*, 2017). Exenatide is a drug used to treat patients with diabetes. It improves insulin sensitivity and also has direct neuroprotective effects (Li *et al.*, 2009). Enhancing neuronal glycolysis is another potential therapeutic approach for PD. Glucose phosphate isomerase 1, an initial enzyme in glycolysis, mediates genetic modification of α-synuclein misfolding by modulating the DAF-16/FOXO pathway, resulting in neuroprotection (Knight *et al.*, 2014). This study suggests a key role of energy-metabolism-associated genes in modifying α-synuclein-induced neurodegenerative processes. In postmortem human PD brains, down-regulation of PPP enzymes and reduced NADPH are found in the putamen and cerebellum (Dunn *et al.*, 2014). Upregulation of G6PD, a rate-limiting enzyme of the PPP, in microglia promotes lipopolysaccharide-induced dopaminergic neurodegeneration by amplifying the inflammatory response, which suggests that targeting G6PD may be promising for PD interventions (Tu *et al.*, 2019). The activation of NADPH oxidase, a superoxide-producing enzyme, causes dopaminergic neurodegeneration and impairments of learning, memory, and motor functions in PD, which can be blocked by apocynin, resulting in neuroprotection via suppression of oxidative stress and neuroinflammation (Hou *et al.*, 2019). Enhancing phosphoglycerate kinase 1 activity with terazosin promotes glycolysis and ATP generation, which can slow neuronal loss and PD progression (Cai *et al.*, 2019). Modulating brain metabolism is an important strategy for PD therapy.

5.4. Huntington's disease

5.4.1. Hypometabolism in striatum—Huntington's disease (HD) is a dominantly inherited neurodegenerative disease involving the loss of striatal neurons and progressive chorea, dementia, and psychological disturbance. The *Huntingtin* gene mutation, with a CAG repeat expansion, is predominantly expressed in the medium spiny neurons of the striatum (Ross *et al.*, 2017). Hypometabolism in the striatum is related to disease severity in patients with early symptomatic HD (Gaura *et al.*, 2017; López-Mora *et al.*, 2016). In contrast, hypermetabolism in some brain regions (inferior parietal and temporal lobules, dentate nucleus, anterior cingulate, and motor regions of the cerebellum) is found to be relevant to more serious hyperkinetic symptoms (Gaura *et al.*, 2017). In preclinical HD gene carriers, elevated glucose metabolism in the thalamus may be a compensatory mechanism for early lesions in the striatum (Feigin *et al.*, 2007). Early metabolic changes in HD may cause later neurodegenerative progress and pose interesting targets for early therapies.

5.4.2. Astrocyte-derived metabolic abnormalities in HD—The early pathological cascade of HD is characterized by a failure in brain energy metabolism. Mutant huntingtin

protein inhibits mitochondrial complex II function, disrupts Ca^{2+} buffering capacity in mitochondria, increases oxidative stress, impairs mitochondrial bioenergetics, trafficking, and dynamics, and reduces creatine kinase (Duan *et al.*, 2014). Decreased GLUT3 expression in neurons causes energy decline in HD mice (Solís-Maldonado *et al.*, 2018). While mutant huntingtin protein does not directly alter glucose metabolism in neurons, it does result in abnormal neuron-astrocyte signaling (Boussicault *et al.*, 2014; Hamilton *et al.*, 2015). Coculture of neurons with astrocytes with mutant huntingtin increases oxidative stress in neurons and reduces neuronal glucose uptake, suggesting the role of neuron-astrocyte signaling transduction in the early metabolic changes of the HD brain (Boussicault *et al.*, 2014). In the striatum, astrocytes account for about 80–90% of cells. The low glucose environment in the brain of HD model animals forces astrocytes in the striatum to use endogenous fatty acids for energy support. Metabolism of fatty acids requires more oxygen than glycolysis and produces greater ROS, which causes initial impairment of neurons in the striatum (Polyzos *et al.*, 2019). Reducing mutant huntington protein in astrocytes slows HD progression in the mouse HD model (Wood *et al.*, 2019). This evidence suggests that astrocyte-derived metabolic abnormalities may be a direct factor causing neuronal toxicity in the early stage of HD.

5.4.3. Modulation of glucose metabolism for HD treatment—Reduced GLUT3 level is observed in *in vitro* and mouse HD models (Covarrubias-Pinto *et al.*, 2015). Increasing GLUT3 expression and supplementing ascorbic acid stimulated neuronal lactate uptake and improved metabolic imbalance in an HD model (Solís-Maldonado *et al.*, 2018). Manganese ion supplementation promotes glucose uptake in HD-model cells by enhancing insulin/IGF receptor-induced AKT signal (Bryan *et al.*, 2020). Increasing glucose uptake and utilization is an important strategy for HD treatment.

6. Concluding remarks

The brain is composed of various specialized cell populations with distinct metabolic profiles, which contribute to region-specific metabolic features. Brain region-specific impairments of glucose metabolism have been characterized in ischemic brain injury, AD, PD, and HD. Ultimately, the development of a precise cell atlas of the brain and corresponding metabolic mapping will be critical for understanding the metabolism-based physiology and pathology of brain function.

Evidence has indicated the features of glucose metabolism related to neuron–glial interactions are vital for understanding neuropathological processes (Afridi *et al.*, 2020; Boussicault *et al.*, 2014; Morken *et al.*, 2014). Therefore, more investigations may further elucidate the interactions among various types of cells in the brain and potential modulation for therapies in neurological disorders.

Cerebral glucose metabolism can be modulated via multiple signal pathways. The molecules in glucose metabolic pathways are involved in non-energetic functions, such as the antioxidant capacity of metabolites derived from the PPP and metabolism-based microglial activation. The role of glucose metabolism in determining cellular fate includes energetic and non-energetic regulation of cerebral function and neurological disease.

Thus, glucose metabolic crosstalk among different regions, cells, and signal molecules in the brain is central to cerebral function, and disruption of these metabolic networks is involved in neurological disease.

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Highlights

- Specific features of brain glucose metabolism (GM) are identified in different brain regions and cell types.
- Intercellular GM crosstalk together with signal molecules contribute to the energetic and non-energetic function in brain.
- Brain GM dysfunction is associated with neurologic pathology including ischemic brain injury and neurodegenerative disorders.
- Targeting GM is promising for treating neurological diseases.

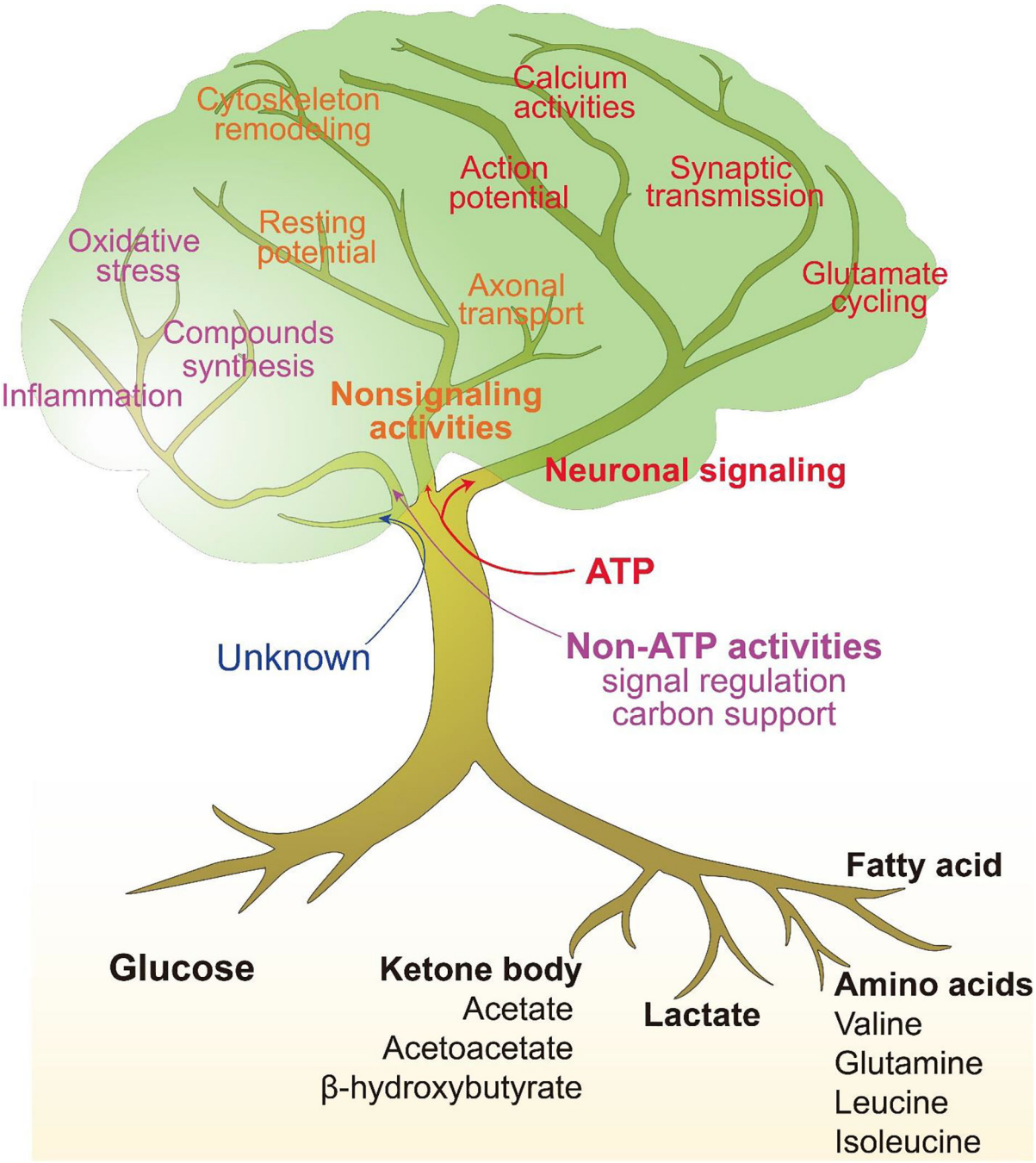

Figure 1.

Energetic fuels supporting the ATP-dependent and ATP-independent actions in the brain. Glucose is the most important fuel for the brain to fulfill complex neurological functions including neuronal signal transmission (action potential, calcium activities, synaptic transmission, and glutamate cycling), and non-signaling activities (axonal transport, resting potential, and cytoskeleton remodeling). Additionally, glucose metabolism provides the carbon for the synthesis of nucleic acids, fatty acids, and amino acids. Glucose metabolites, such as NADPH, are involved in the regulation of inflammation and redox reaction. Aside

from glucose, alternative fuels such as ketone bodies, lactate, fatty acids, and amino acids, are used by the brain, particularly in response to stress, to maintain brain functions.

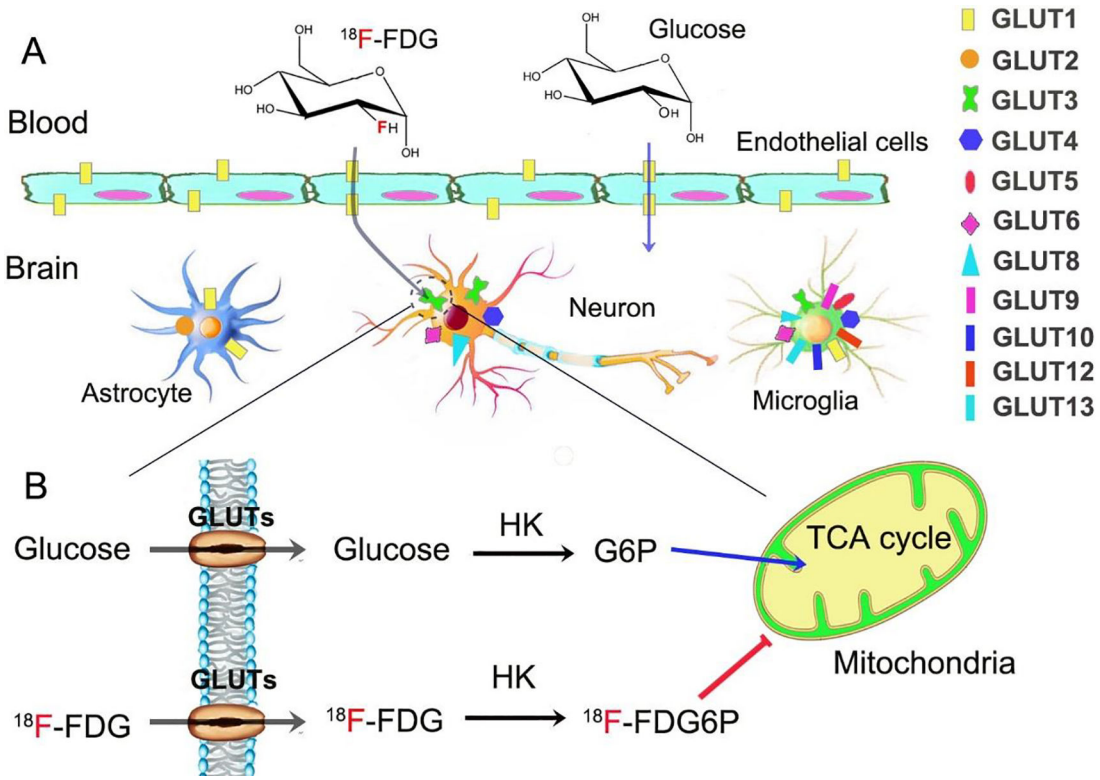

Figure 2.

Glucose transporter (GLUT) expression in brain cells and the role in glucose or fluorodeoxyglucose F18 (^{18}F-FDG) transport into cells. (A) Distinct expression of GLUTs in vascular endothelial cells, neurons, astrocytes, and microglia. (B) ^{18}F-FDG is transported into brain tissue by GLUTs and is phosphorylated to ^{18}F-FDG-6-phosphate by HK. FDG is not further metabolized but remains trapped and can be detected in cells for evaluating brain glucose uptake. TCA, tricarboxylic acid; HK, hexokinase; G6P, glucose 6-phosphate.

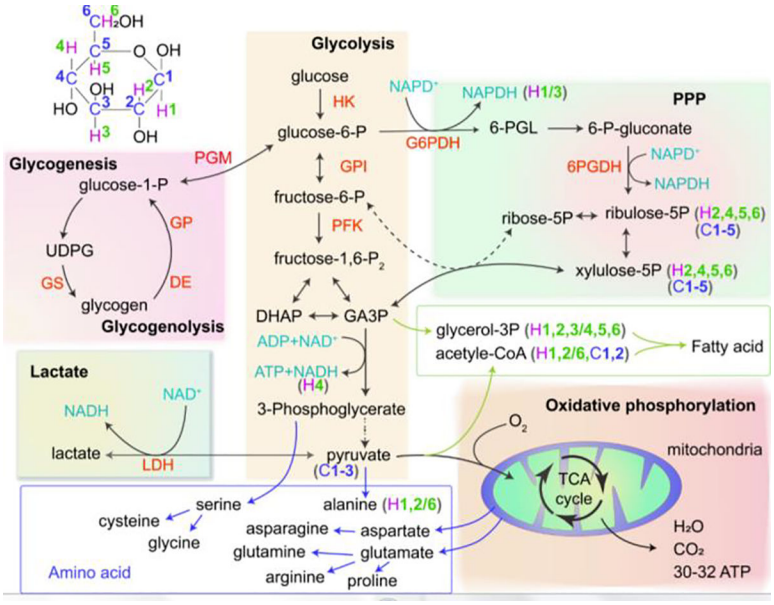

Figure 3.

Pathways of glucose metabolism for ATP production and synthesis of biological compounds. The glycolytic (oxygen-independent) and mitochondrial tricarboxylic acid (TCA) cycle (oxygen dependent) pathways contribute to ATP generation for energetic support in the brain. Additionally, glucose-6-P can enter into the pentose phosphate pathway (PPP) for producing NADPH, regulating redox reaction, and providing a source of nucleotides. Glucose can be stored primarily in astrocytes as glycogen in response to stress. Additionally, glucose metabolites 3-phosphoglycerate and pyruvate are implicated in the synthesis of amino acids, directly or indirectly, via the TCA cycle. GA3P contributes to the synthesis of fatty acids and nucleic acids. The H(1–6) and C(1–6) atoms in glucose can be traced to different metabolites. C(1–3) atoms in glucose enter into pyruvate and C(1–5) and access the PPP pathway. H atoms are widely distributed in nucleic acids, fatty acids, and amino acids. HK, hexokinase; GPI, glucose-6-phosphate isomerase; PFK, phosphofructokinase; DHAP, dihydroxyacetone phosphate; GA3P, glyceraldehyde-3-phosphate; G6PDH, glucose-6-phosphate dehydrogenase; 6-PGL, 6-phosphoglucono-d-lactone; PGM, phosphoglucomutase; GS, glycogen synthase; DE, debranching enzyme; GP, glycogen phosphorylase; LDH, lactate dehydrogenase.

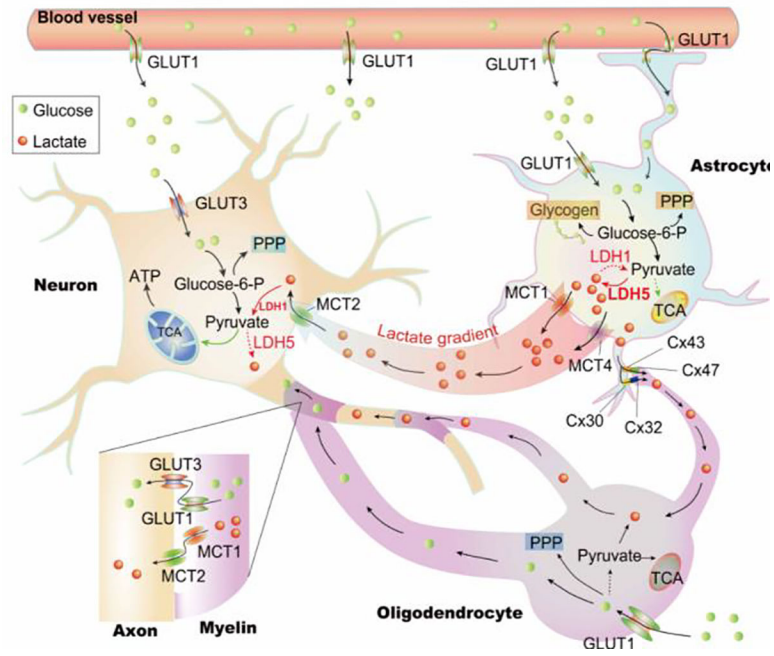

Figure 4.

Astrocyte-neuron-oligodendrocyte energy metabolism interactions. Glucose in neurons is primarily used for ATP production and is metabolized into lactate in astrocytes. The glucose transporters (GLUTs) mediate the transportation of glucose into cells. GLUT1, located in cerebral endothelial cells, transits glucose from the blood into the brain tissue. GLUT1 also mediates the entrance of glucose into astrocytes and oligodendrocytes. Glucose is transported into neurons via GLUT3. Monocarboxylate transporters (MCTs) and connexin (Cx) contribute to astrocyte-neuron-oligodendrocyte lactate transport. MCT1 and MCT4 in astrocytes release lactate, which diffuses into neurons due to the lactate gradient and is actively taken up by neurons via the MCT2. Additionally, MCT1 in the myelin cooperates with MCT2 in the axon to translate the lactate from oligodendrocytes to neurons. Therefore, glucose and lactate, together with their transporters, contribute to the astrocyte-neuron-oligodendrocyte energy metabolism interactions. TCA, tricarboxylic acid; PPP, pentose phosphate pathway; LDH, lactate dehydrogenase.

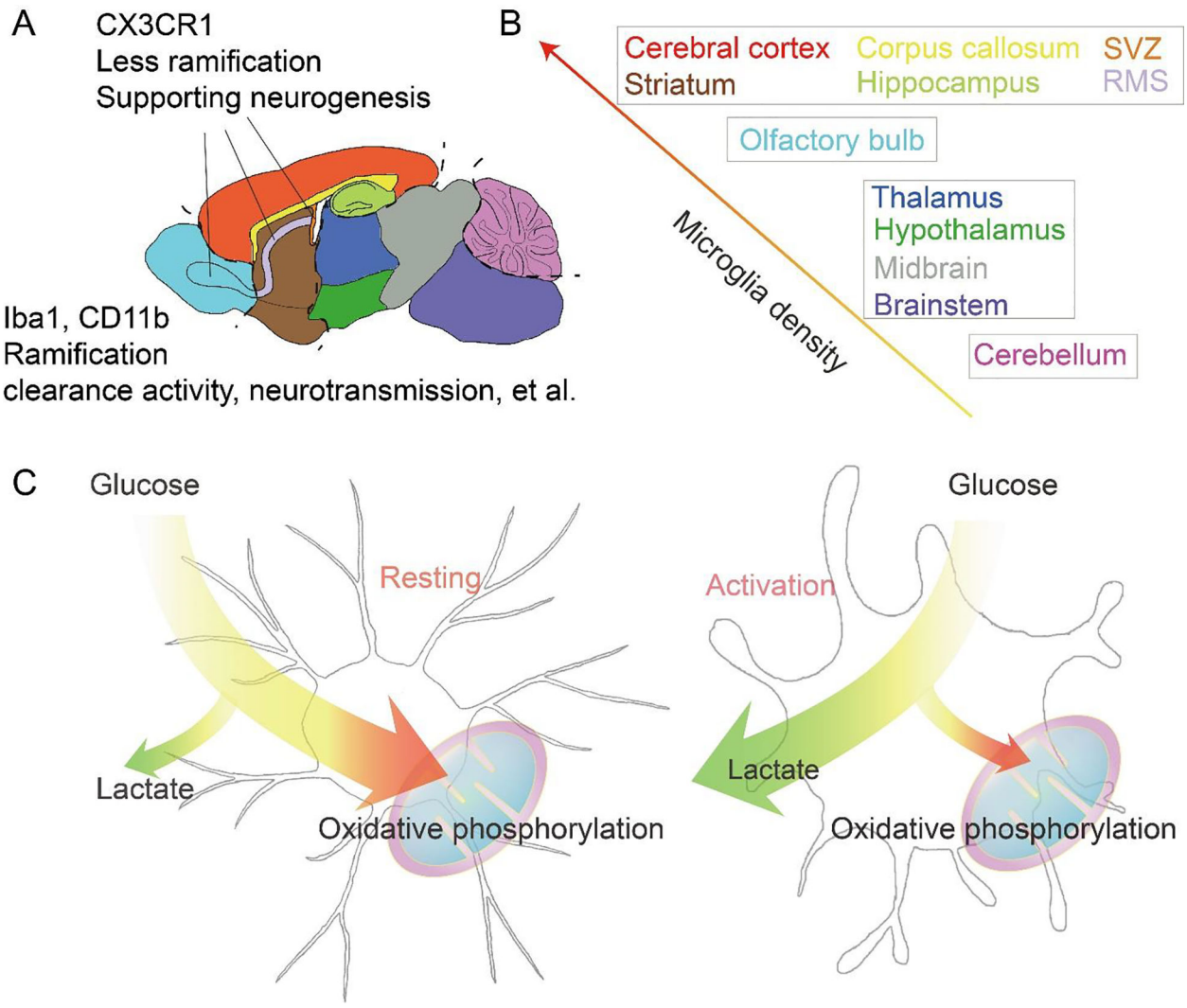

Figure 5.

Microglia in the brain and glucose metabolism. (A, B) The distinct cellular structure, function, and density of microglia across different mouse brain areas. CX3CR1 positive microglia, which have less ramification and are primarily distributed in the olfactory bulb, RMS, and SVZ, support neurogenesis. In contrast, Iba1 and CD11b positive microglia, which have obvious ramification, are widely distributed in the whole brain and account for the clearance and neurotransmission. Microglial density gradually increases from the cerebellum posteriorly, forward to the cortex. (C) Glucose in resting microglia primarily enters into mitochondrial oxidative phosphorylation. In contrast, activated microglia primarily use glucose for lactate production. RMS: rostral migratory stream. SVZ: subventricular zone.

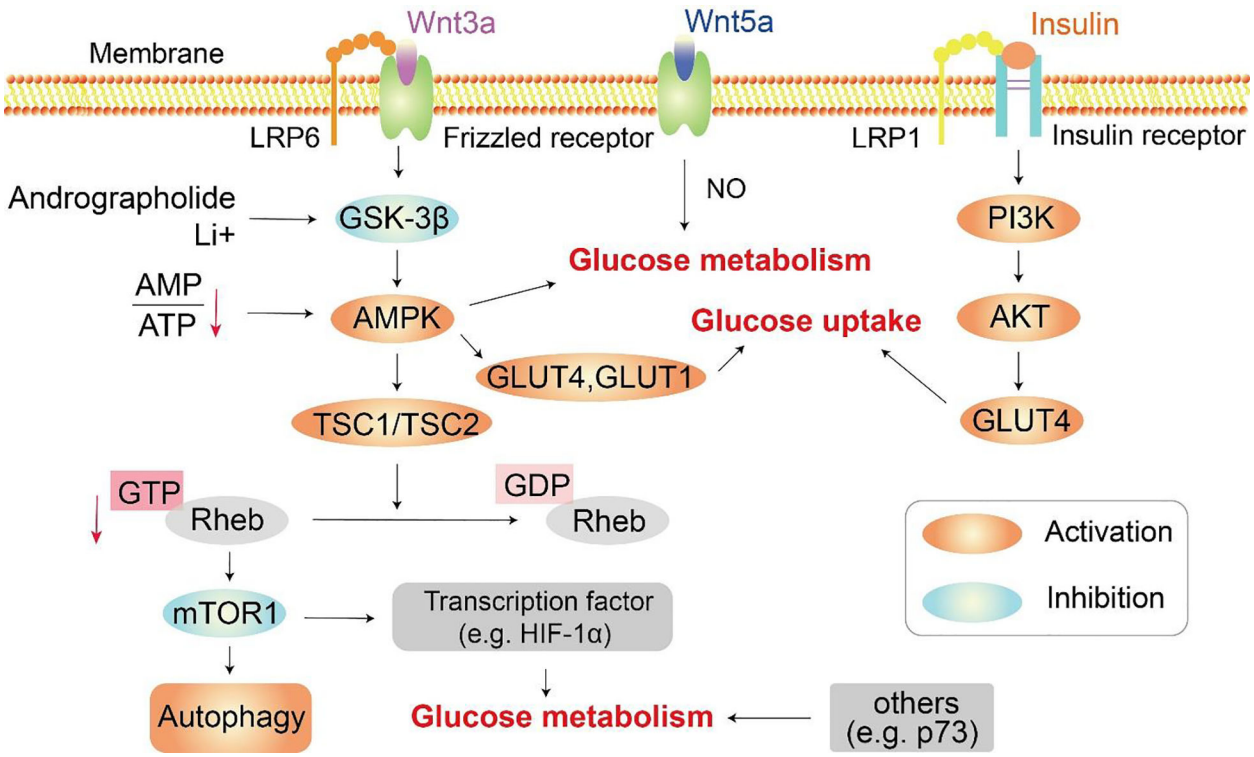

Figure 6.

Signaling pathways that modulate cerebral glucose metabolism. Frizzled receptors located in the cellular membrane can conjugate with Wnt ligands to activate the GSK-3β/AMPK/GLUTs pathway or GSK-3β/AMPK/TSC/mTOR pathway, which regulate glucose uptake and metabolism. Moreover, insulin can activate the PI3K/AKT pathway to modulate glucose metabolism. LRPs assist both frizzled receptors and insulin receptors to bind to their ligands. LRP, lipoprotein receptor-related protein; NO, nitric oxide; GSK-3β, glycogen synthase kinase; AMPK, AMP-activated protein kinase; GLUT, glucose transporter; TSC, Tuberous sclerosis; Rheb, Ras homolog enriched in the brain; mTOR, mammalian target of rapamycin; Hif-1α, hypoxia-inducible factor 1α.

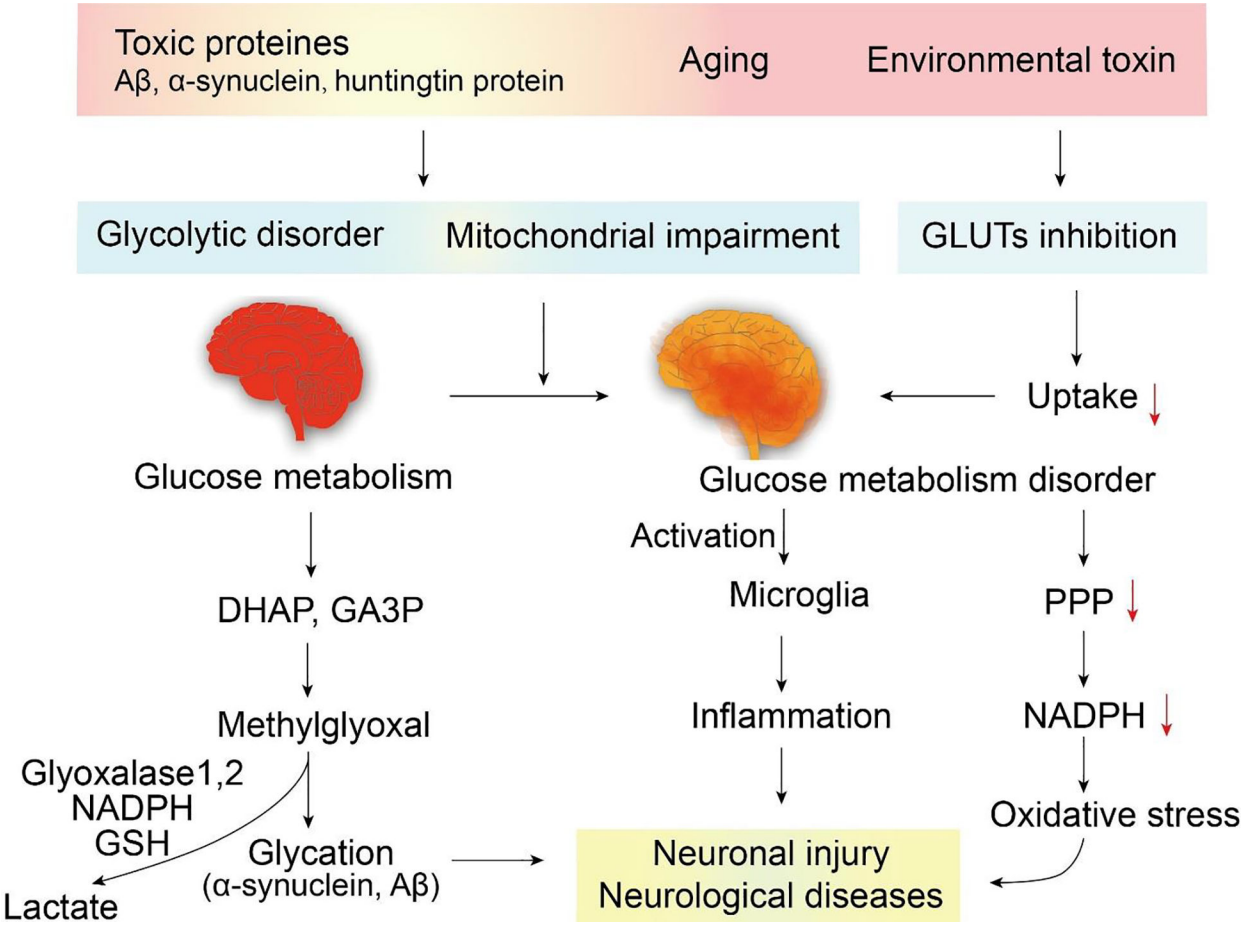

Figure 7.

Glucose metabolism-mediated signal regulation in neurological disease. Disease-related gene mutation, aging, or environmental toxins can cause dysfunction of glucose metabolism in the brain, which leads to neuronal injury by activating inflammation or promoting oxidative stress and the accumulation of glycated toxic proteins (such as α-synuclein, Aβ), impairing neuronal function. Aβ, amyloid beta; GLUT, glucose transporter; PPP, pentose phosphate pathway; DHAP, dihydroxyacetone phosphate; GA3P, glyceraldehyde-3-phosphate; GSH, glutathione.

Table 1

Altered brain glucose metabolism in neurological diseases

Diseases	Brain glucose metabolism	FDG uptake in PET	References
Focal ischemic stroke	Infarct area: hypometabolism	Infarct area: reduction, Peri-ischemic region: elevation	(Walberer *et al.*, 2012; Yuan *et al.*, 2013)
CA-induced global brain ischemia	Cortex: hypometabolism HK I and II levels reduction	Whole brain reduction, particularly in the occipital cortex, putamen, and white matter	(Hahn *et al.*, 2014; Li *et al.*, 2015; Putzu *et al.*, 2018)
Alzheimer's disease	Hypometabolism in injured brain regions Reduction of glycolysis and PPP; Cortex: glucose transport reduction with decreased levels of GLUT1 and GLUT3; Microglia: oxidative phosphorylation decrease, aerobic glycolysis increase	Reduction in bilateral temporal lobes, precuneus, parahippocampal gyrus, posterior cingulate gyrus, parietal lobe, temporoparietal and posterior cingulate regions	(Baik *et al.*, 2019; Butterfield and Halliwell, 2019; Dave *et al.*, 2020; Demarest *et al.*, 2020; Gordon *et al.*, 2018; Shivamurthy *et al.*, 2015; Szablewski, 2017; Winkler *et al.*, 2015)
Dementia with Lewy bodies	Hypometabolism in injured brain regions	Reduction in occipital cortex, precuneus, temporal and parietal cerebral cortexes, parietotemporal, posterior cingulate, and frontal association cortices	(Dave *et al.*, 2020; Ishii, 2014; Shivamurthy *et al.*, 2015)
Frontotemporal dementia	Hypometabolism in injured brain regions	Reduction in the frontal lobe, anterior temporal lobe, anterior cingulate gyrus, ventromedial frontopolar cortex, bilateral prefrontal areas, and subcortical structures, including the basal ganglia (putamen and globus pallidus) and medial thalamic regions	(Dave *et al.*, 2020; Ishii, 2014; Shivamurthy *et al.*, 2015)
Dementia vascular dementia	Hypometabolism in injured brain regions	Reduction in focal cortical and subcortical, deep gray nuclei, cerebellum, primary cortexes, middle temporal gyrus, and anterior cingulate cortex	(Shivamurthy *et al.*, 2015)
Parkinson's disease	Hypometabolism Reduction of pyruvate kinase 2 activity; Glycolysis impairment; Mitochondrial metabolic impairment	Reduction in parietal cortex, putamen, caudate nucleus and inferior parietal lobule	(Bogetofte *et al.*, 2019; Firbank *et al.*, 2017; Knight *et al.*, 2014; Liu *et al.*, 2016; Meles *et al.*, 2017; Ruppert *et al.*, 2020)
Huntington's disease	Hypometabolism and hypermetabolism Mitochondrial complex II inhibition Creatine kinase reduction GLUT3 expression reduction	Reduction in striatum Elevation in inferior parietal and temporal lobules, dentate nucleus, anterior cingulate, and motor regions of the cerebellum	(Gaura *et al.*, 2017; López-Mora *et al.*, 2016) (Duan *et al.*, 2014; Solís-Maldonado *et al.*, 2018)

FDG: fluorodeoxyglucose; PET: positron emission tomography; CA: cardiac arrest; HK: hexokinase; PPP: pentose phosphate pathway; GLUT: glucose transporters

Table 2

Chemicals regulating cerebral glucose metabolism

Chemicals	Function	References
Cytochalasin B	GLUT1-4 inhibitor	(Díaz-García *et al.*, 2017; Kapoor *et al.*, 2016)
Stf31	GLUT1 inhibitor	(Wang *et al.*, 2019b)
Phloretin	GLUT-1 inhibitor	(Kilic *et al.*, 2018)
Oxamate	LDH inhibitor	(Abraham *et al.*, 2018)
Carbenoxolone	Connexin 30 and connexin 43 gap junction inhibitor	(Yin *et al.*, 2018)
α-cyano-4-hydroxy-cinnamate	MCT1,2,4 inhibition, mitochondrial pyruvate carrier inhibition	(Matsui *et al.*, 2017; Perez-Escuredo *et al.*, 2016)
AR-C155858	MCT1 and MCT2 inhibition	(Le Douce *et al.*, 2020; Perez-Escuredo *et al.*, 2016)
4,4'-dibenzamidostilbene-2,2'-disulphonate	MCT2 inhibitor	(Perez-Escuredo *et al.*, 2016)
7-(N-benzyl-N-methylamino)-2-oxo-2H-chromene-3-carboxylic acid	MCT1 inhibitor (inhibiting lactate uptake)	(Perez-Escuredo *et al.*, 2016)
5-nitro-2-(3-phenylpropylamino)-benzoate	MCT1 and MCT4 inhibitor	(Perez-Escuredo *et al.*, 2016)
AZD3965	MCT1 and MCT2 inhibitor	(Perez-Escuredo *et al.*, 2016)
1,4-dideoxy-1,4-imino-D-arabinitol	Glycogen phosphorylation inhibitor (inhibiting glycogen synthesis)	(Kilic *et al.*, 2018; Matsui *et al.*, 2017)
Isofagomine	Glycogen phosphorylase inhibitor	(Choi *et al.*, 2019)
Gintonin	Activating lysophosphatidic acid receptors (promoting glycogen synthesis)	(Choi *et al.*, 2019)
6-amino nicotinamide	Glucose-6-phosphate dehydrogenase inhibitor (PPP inhibition)	(Tu *et al.*, 2019)
Dehydroepiandrosterone	Glucose-6-phosphate dehydrogenase inhibitor (PPP inhibition)	(Tu *et al.*, 2019)
AP-III-a4	Enolase inhibitor	(Jung *et al.*, 2013)

GLUT, glucose transporter; MCT, monocarboxylate transporter; PPP, pentose phosphate pathway.