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Astrocytes as Key Regulators of Brain Energy Metabolism: New Therapeutic Perspectives

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Astrocytes play key roles in the regulation of brain energy metabolism, which has a major impact on brain functions, including memory, neuroprotection, resistance to oxidative stress and homeostatic tone. Energy demands of the brain are very large, as they continuously account for 20–25% of the whole body's energy consumption. Energy supply of the brain is tightly linked to neuronal activity, providing the origin of the signals detected by the widely used functional brain imaging techniques such as functional magnetic resonance imaging and positron emission tomography. In particular, neuroenergetic coupling is regulated by astrocytes through glutamate uptake that triggers astrocytic aerobic glycolysis and leads to glucose uptake and lactate release, a mechanism known as the Astrocyte Neuron Lactate Shuttle. Other neurotransmitters such as noradrenaline and Vasoactive Intestinal Peptide mobilize glycogen, the reserve for glucose exclusively localized in astrocytes, also resulting in lactate release. Lactate is then transferred to neurons where it is used, after conversion to pyruvate, as a rapid energy substrate, and also as a signal that modulates neuronal excitability, homeostasis, and the expression of survival and plasticity genes. Importantly, glycolysis in astrocytes and more generally cerebral glucose metabolism progressively deteriorate in aging and age-associated neurodegenerative diseases such as Alzheimer's disease. This decreased glycolysis actually represents a common feature of several neurological pathologies. Here, we review the critical role of astrocytes in the regulation of brain energy metabolism, and how dysregulation of astrocyte-mediated metabolic pathways is involved in brain hypometabolism. Further, we summarize recent efforts at preclinical and clinical stages to target brain hypometabolism for the development of new therapeutic interventions in age-related neurodegenerative diseases.

Keywords: astrocytes, lactate, glucose, brain, energy, metabolism, new therapeutic approach, GliaPharm

INTRODUCTION

The brain requires high amounts of energy to function. As a result, 20–25% of the energy consumed by the human body is dedicated to cerebral functions, although the brain only represents 2% of the total body mass. Maintenance and restoration of neuronal ion gradients and synaptic transmission, as well as uptake and recycling of neurotransmitters are the major contributors to these energy demands (Riveros et al., 1986; Wong-Riley, 1989; Attwell and Laughlin, 2001; Alle et al., 2009; Hyder et al., 2013; Magistretti and Allaman, 2016; Yu et al., 2018). Glucose is the main energy substrate in the adult brain. However, other sources of energy can be used under particular circumstances, such as ketone bodies that are consumed during development and fasting, and

lactate that can be preferentially used during periods of intense physical activity (Owen et al., 1967; Nehlig, 2004; Rasmussen et al., 2011; Chowdhury et al., 2014; Magistretti and Allaman, 2018). Importantly, when plasma lactate concentrations rise, central nervous system (CNS) lactate levels also increase, which is correlated with decreased glucose uptake, and indicating a preferential utilization of lactate over glucose as brain energy source (Smith et al., 2003).

Several neurodegenerative diseases linked to aging are characterized by a decrease in the consumption of energy by the brain in specific regions. These include, among others, Alzheimer's disease (AD), Parkinson's disease (PD), Frontotemporal dementia (FTD), Amyotrophic lateral sclerosis (ALS), depression and certain neurodevelopmental disorders. Hypometabolism also occurs in physiological aging, a fact that may participate in the vulnerability of the nervous system to pathological states of aging. Decreased energy availability for neurons results in neurodegeneration, cognitive impairment, as well as abnormalities in neuronal function and excitability (Muddapu et al., 2020). Astrocytes, a type of glial cells in the brain, support essential functions such as maintenance of neurotransmitter pools, trophic support, metabolism, synaptic formation and plasticity, myelin sheath formation, injury healing, and immune surveillance (Burda et al., 2016; Manninen et al., 2020). They are key in regulating neurometabolic and neurovascular couplings, thereby linking neuronal activity to brain energy consumption. In particular, astrocytes respond to neuronal activity by taking up glutamate at the synapse, which triggers aerobic glycolysis and lactate secretion. Then, lactate can be used by neurons as preferred energy source upon activity, as formulated by the astrocyte-neuron lactate shuttle (ANLS) model (Pellerin and Magistretti, 1994; Belanger et al., 2011; Magistretti and Allaman, 2018). Astrocytes also modulate activity-dependent vasodilation through nitric oxide-mediated pathways (Bonvento et al., 2002).

In this review, we discuss the different roles played by astrocytes in the control of brain energy metabolism and homeostasis, and how these pathways are affected in aging and hypometabolic neurodegenerative diseases such as AD. Further, we review the current therapeutic strategies from *in vitro*, *in vivo*, and clinical evidence that aim at restoring brain energy deficits in neuropathologies with metabolic dysfunctions.

ASTROCYTE-MEDIATED METABOLIC SUPPORT

Under normal homeostatic conditions, the supply and demand of energy are tightly coupled. For instance, cerebral blood flow (CBF) and glucose utilization increase in response to neuronal activity through processes known as neurovascular and neurometabolic couplings (Belanger et al., 2011). These processes constitute the bases of functional brain imaging techniques, among which positron emission tomography (PET) that allows determination of CBF, cerebral metabolic rate of glucose consumption (CMRglc), cerebral metabolic rate of oxygen consumption CMRO2, as well as functional magnetic

resonance imaging (fMRI) that measures brain oxygenation and blood volume (Magistretti and Pellerin, 1996; Raichle and Mintun, 2006; Figley and Stroman, 2011; Roumes et al., 2021).

Astrocytes have unique cytoarchitectural features that ideally position them to sense their surrounding environment and dynamically respond to extracellular changes (Belanger et al., 2011). They possess numerous processes that form highly organized anatomical domains interconnected through functional networks via gap junctions. Some of these processes closely ensheath synapses, whereas others are in contact with brain capillaries (Iadecola and Nedergaard, 2007; Oberheim et al., 2009; Mathiisen et al., 2010). At the synapse level, astrocytes' perisynaptic processes express glutamate transporters that can sense changes in neuronal activity, while at the vasculature level, luminal surface of their endfeet that is in contact with vascular endothelium express glucose transporter 1 (GLUT1) (Patching, 2017), that will allow facilitated diffusion of glucose into astrocytes, to supply energy upon neuronal activity. Finally, astrocytes can release vasoactive substances to act on brain glucose supply depending on neuronal activity state (Belanger et al., 2011; MacVicar and Newman, 2015).

Neurons and astrocytes possess distinct metabolic profiles. In the presence of oxygen, neurons process glucose in an oxidative way to yield ATP through mitochondrial activity, while glucose entering astrocytes preferentially undergoes glycolysis to produce pyruvate and lactate (Magistretti and Allaman, 2015; Supplie et al., 2017). Astrocytes specifically express glycolytic enzymes, which make them utilize 80% of the glucose through glycolysis. In neurons, glycolytic enzymes, such as 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) and pyruvate dehydrogenase kinase 4 (PDK4) are inhibited, which make them highly phosphorylative cells (Magistretti and Allaman, 2018). Furthermore, astrocytes preferentially express lactate dehydrogenase 5 (LDH5), which favors the conversion of pyruvate into lactate, while neurons exclusively express lactate dehydrogenase 1 (LDH1) that favors conversion of lactate into pyruvate (Bittar et al., 1996). Astrocytes also have higher NADH to NAD^+ ratio than neurons, which favors the reduction of pyruvate into lactate (Mongeon et al., 2016). Interestingly, inhibiting mitochondrial activity specifically in astrocytes did not have any phenotypic effect in mice (Supplie et al., 2017). In contrast, enhancing glycolysis in neurons led to dramatic decrease in glucose utilization in the pentose phosphate pathway, increased oxidative stress and apoptosis (Herrero-Mendez et al., 2009). These studies highlight the cellular specificity of distinct metabolic pathways in the brain with astrocytes being predominantly glycolytic, while neurons are oxidative.

As formulated by the ANLS, glutamate is taken up by astrocytes and recycled through the glutamate-glutamine cycle (Bak et al., 2006; McKenna, 2007). This process, which is mediated by astrocytic Na^+-dependent glutamate transporters, leads to increases in cytosolic Na^+ that activates Na^+/K^+ ATPase, thereby increasing ATP consumption (Magistretti and Chatton, 2005) and stimulation of GLUT1 activity (Porras et al., 2008). In turn, glycolysis is activated and results in enhanced glucose uptake in astrocytes and release of lactate toward neurons (Pellerin and Magistretti, 2012). Under resting

conditions, astrocytes release 85% of the glucose they consume in the form of lactate (Bolanos et al., 1994). An *in vivo* study using two photon microscopy and lactate fluorescence resonance energy transfer (FRET) nanosensors confirmed lactate gradient between astrocytes and neurons (Machler et al., 2016). Another level of astrocyte-neuron metabolic coupling is through the activity-dependent production of NH4+ in neurons that, upon transfer to astrocytes, favors astrocytic glycolysis. Thus, in neurons, conversion of glutamine into glutamate by phosphate activated glutaminase (PAG) leads to the production of NH4+, which can be transferred to astrocytes through transporters and K^+ channels (Kelly and Rose, 2010). In astrocytes, NH4+ can enter the mitochondria and acidifies mitochondrial matrix, which in turn inhibits mitochondrial incorporation of pyruvate that depends on the H^+-coupled mitochondrial pyruvate carrier (MPC) (Herzig et al., 2012; Lerchundi et al., 2015).

Lactate is a metabolic end-product that cannot directly be used and requires its conversion into pyruvate to serve as energy and carbon source to the tricarboxylic acid (TCA) cycle (Barros et al., 2020). One of the advantages of producing lactate that is not readily consumed is to allow its distribution and exchanges between lactate producing and lactate consuming cells (Brooks, 2018). Importantly, lactate also serves as a signaling molecule that modulates mechanisms underlying synaptic plasticity and memory consolidation through the regulation of plasticity genes expression (Suzuki et al., 2011; Yang et al., 2014; Margineanu et al., 2018). Neuroprotective effects of lactate have been demonstrated in various types of brain damages, including ischemic (Schurr et al., 2001; Smith et al., 2003), excitotoxic and mechanical insults (Ros et al., 2001; Cureton et al., 2010). The transfer of lactate between cells is specific and controlled by monocarboxylate transporters (MCTs). There are different types of MCTs that are differentially expressed between producing and receiving cells and have different affinities for lactate. For instance, neurons exclusively express high-affinity MCT2, while astrocytes express lower-affinity MCT1 and MCT4 (Roosterman and Cottrell, 2020). Some studies shown that MCT2 expression in neurons is co-localized with glutamate receptors at the postsynaptic membranes of fast acting excitatory synapses, further supporting the intracellular signaling roles of lactate (Bergersen et al., 2001, 2005). Since lactate is co-transported through MCTs with H^+, regulation of pH is essential for the transport of lactate (Bosshart et al., 2019). Lactate symbiosis between astrocytes and neurons is also well demonstrated through the role of energy sensor AMP-activated protein kinase (AMPK). Thus, intracerebral levels of lactate were found to be decreased in AMPK-deficient mice, which was concomitant with decreased glycolysis, oxidative phosphorylation and neuronal survival (Muraleedharan et al., 2020). Mechanistically, phosphorylation of AMPK in astrocytes was found to destabilize thioredoxin-interaction protein (TXNIP), which led to the translocation of GLUT1 at the plasma membrane, glucose uptake and lactate production that in turn provided neuroprotection in a non-cell-autonomous manner (Muraleedharan et al., 2020). The lactate signaling may also occur through the activation of the lactate responsive-G-protein-coupled receptor 81 (GPR81) (Lauritzen et al., 2014; Morland et al., 2015). Activation of GPR81

triggers Gi-mediated pathway that in turn inhibits Adenylate cyclase (AC), resulting in a decrease in cyclic AMP (cAMP) levels and changes in numerous intracellular mechanisms (Ahmed et al., 2009, 2010).

In a key study by Suzuki et al. (2011), transfer of lactate from astrocytes to neurons was found to be critical to mediate synaptic plasticity and memory consolidation. Pharmacological inhibition or genetic targeting of MCT2 irreversibly impairs long-term memory in mice (Newman et al., 2011; Suzuki et al., 2011). Long-term memory impairment could be reversed in MCT4-deficient mice by intrahippocampal administration of lactate, but not glucose (Suzuki et al., 2011). These results indicate that the neuronal uptake of lactate is important for the establishment of long-term memories. Further, degradation of glycogen, which, in the brain, is exclusively localized in astrocytes, is required for memory formation (Newman et al., 2011; Suzuki et al., 2011). Interestingly, exercise-mediated lactate increase was shown to enhance lactate levels in the hippocampus and to be beneficial for memory in mice (El Hayek et al., 2019). Activation of astrocytic, but not neuronal, β2-adrenergic receptors led to lactate production that mediated memory formation (Gao et al., 2016; Dong et al., 2017). Furthermore, lactate mediates neuroprotective effects following traumatic brain injury (TBI) (Alvarez et al., 2014; Zhou et al., 2018), hypoxia (Schurr et al., 1997), cerebral ischemia, and glutamate-mediated excitotoxicity (Bliss et al., 2004; Berthet et al., 2009; Jourdain et al., 2016) and was found to promote adult hippocampal neurogenesis (Lev-Vachnish et al., 2019). Interestingly, lactate has a dual impact on NMDA receptors. With low glutamate, lactate stimulates NMDA receptor signaling, resulting in plasticity gene induction and memory consolidation. However, in excitotoxic conditions with high glutamate, lactate decreases NMDA receptor-mediated signaling, thereby preventing glutamate-induced neuronal death (Jourdain et al., 2018). Recent evidence *in vivo* indicates that lactate is preferred to glucose as an energy substrate in active neurons, and that lactate metabolism shapes neuronal activity through K_{ATP} channels (Karagiannis et al., 2021). An important study finally showed that the effect of circulating glucose on neuronal depolarization was exclusively mediated by astrocyte-mediated lactate release, providing strong evidence for the role of ANLS *in vivo* (Sada et al., 2015).

BRAIN ENERGY METABOLIC DYSFUNCTIONS IN AGING AND NEURODEGENERATIVE DISEASES

Aging leads to many physiological changes in body functioning, including cerebral and cognitive functions such as decreased working, spatial and episodic memory (Mattay et al., 2006; Glisky, 2007). With age, aerobic glycolysis and consumption of glucose were found to be severely decreased in the brain, particularly in the temporal, parietal and frontal lobes, and motor cortex (Goyal et al., 2017). This is accompanied in normal aging by the degeneration of brain structures, leading to loss in brain weight and volume (Dekaban, 1978; Fox and Schott, 2004), cortical thickness in the prefrontal cortex, medial temporal lobe and

hippocampus (Sowell et al., 2003; Salat et al., 2004), gray matter atrophy, disruptions of white matter integrity (Bi et al., 2021), and synaptic density (Masliah et al., 1993). These non-pathological changes contribute to age-related cognitive decline in elderly subjects (Resnick et al., 2003; Yang et al., 2015; Bender et al., 2016).

Advances in neuroimaging techniques, such as MRI and PET allow to investigate the dynamic brain changes with aging *in vivo*. For instance, brain network connectome, which is assessed through diffusion MRI tractography efficiency, was found to decline with age in specific brain regions such as the hippocampus, thalamus, and frontal and parietal cortices (Bi et al., 2021). Glucose hypometabolism was observed with aging in the anterior cingulate cortex, several parts of the orbital and frontal gyrus and in the thalamus (Bi et al., 2021). By combining these two measurements, the study revealed a close coupling between age-dependent decreased brain network connectome and hypometabolism in specific brain regions that include frontal and temporal lobes, cingulate gyrus, hippocampus and hypothalamus (Gong et al., 2009; Bi et al., 2021). Importantly, several studies showed that glucose hypometabolism is due to a decrease of brain aerobic glycolysis as measured by the difference between glucose and oxygen consumptions (Goyal et al., 2017; Hipkiss, 2019; Tang, 2020; Yan et al., 2020). Both animal models and human studies showed that aging is characterized by a decreased aerobic glycolysis in astrocytes (Goyal et al., 2017) and mitochondrial oxidative phosphorylation in neurons (Boumezbeur et al., 2010; Jiang and Cadenas, 2014). It has been proposed that pathological neurons first exhibit mitochondrial dysfunction and compensatory increase in oxidative phosphorylation that results in a competition for a limited energetic resource, i.e., astrocyte-derived lactate, as the fuel of oxidative phosphorylation (Demetrius and Driver, 2015). This competition for energetic resource leads to deleterious consequences on initially healthy neurons in the vicinity of neurons with mitochondrial dysfunction, thereby spreading neurodegeneration and development of the pathological state, from normal aging to neurodegeneration (Demetrius et al., 2014). At the cellular level, impaired glucose uptake is correlated with a decrease in the expression and membrane translocation of the insulin-sensitive neuronal glucose transporters, GLUT3 and GLUT4, which influence neuronal survival in the rat brain (Jiang et al., 2013). Decrease of microvascular endothelium GLUT1 was also observed in the hypometabolic rat brain (Jiang et al., 2013). The disruption in glucose metabolism due to the loss of glucose transporters is closely associated with synaptic dysfunction and renders neurons vulnerable to degeneration.

Alzheimer's disease, the most prevalent cause of age-associated dementia, is a progressive neurodegenerative disease with biochemical, metabolic and physiological changes that impact memory, thinking and behavior. In addition to the historical description of the pathology that include β amyloid plaques and hyperphosphorylated tau in the brain, it is characterized by clear mitochondrial and metabolic impairments (Butterfield and Halliwell, 2019). Hence, AD can be considered as a metabolic disease with impairment in mitochondrial bioenergetics, as well as glucose brain import and metabolism (Zulfiqar et al., 2019).

Brain glucose hypometabolism appears early in the genesis of the pathology and is frequently present before the onset of clinically measurable symptoms (Costantini et al., 2008; Cunnane et al., 2011). For instance, numerous studies have highlighted reduced regional activity-dependent glucose uptake and utilization in AD using ^{18}F-fluorodeoxyglucose (FDG) PET (Ferreira et al., 2010; Demetrius and Driver, 2013; Tomi et al., 2013; Demetrius et al., 2014; Fu and Jhamandas, 2014; Yin et al., 2016; Weise et al., 2018). These decreases are mostly observed in the parieto-temporal and posterior cingulate cortices and extended to the frontal areas while disease advances, whereas primary motor and visual cortices are less severely affected, and cerebellum, thalamus and basal ganglia are relatively spared (Friedland et al., 1985; Koss et al., 1985; Minoshima et al., 1997). In AD, degeneration occurs in the locus coeruleus (LC) depending on the disease progression (Chan-Palay and Asan, 1989; Rub et al., 2001; Wilson et al., 2013; Arendt et al., 2015; Peterson and Li, 2018). Noradrenaline (NA), which is released from the LC, activates cellular response in astrocytes that trigger increase in Ca^{2+} and cAMP, resulting in numerous cellular responses including enhanced aerobic glycolysis (Arendt et al., 2015; Vardjan et al., 2018). Therefore, early destruction of the LC may contribute, at least in part, to the impaired glucose metabolism in AD (Moore and Bloom, 1979). Another study reported a reduction of several glycolysis intermediates in the cerebrospinal fluid (CSF) of AD patients compared with controls (Bergau et al., 2019). In postmortem AD brains, dysregulation of nutrient transporters was observed, with a decrease of neuronal GLUT3 and astrocytic GLUT1 (Simpson et al., 1994; Harr et al., 1995; Mooradian et al., 1997). A similar reduction in GLUT1 and lactate transporters has been reported in culture of astrocytes from AD mouse model (Merlini et al., 2011). Postmortem studies of AD brains also revealed alterations in glycolytic enzymes activity, glucose utilization and amino acid metabolism (Marcus and Freedman, 1997; Palmer, 1999; Butterfield and Halliwell, 2019). Several genes involved in energy regulation were downregulated in AD patients and mouse model of AD (Liang et al., 2008). AD symptoms essentially never occur without glucose hypometabolism, and the extent of these metabolic changes are strongly correlated with the severity of clinical symptoms (Woo et al., 2010; Thomas et al., 2015). Of relevance, mitochondrial dysfunction, which is associated with age-related neurodegeneration, is also particularly important in AD (Beal, 2005; Yao and Brinton, 2011). In line with the decreased glycolysis in AD brains, an interesting recent study showed that levels of lactate were reduced in the CSF of patients with AD, although no correlation were found between CSF lactate and amyloid levels (Bonomi et al., 2021). Recently, physical exercise was found to have beneficial effects in AD through the improvement of brain glucose metabolism. Thus, aerobic exercise leads to the maintenance of brain glucose uptake in mild AD patients (Robinson et al., 2018), and to the protection against hypometabolism in brain regions particularly vulnerable in AD (Dougherty et al., 2017).

In humans, Apolipoprotein E (APOE) exists in three different isoforms: APOE2, APOE3 and APOE4. Homozygous and heterozygous carriers of APOE4 have respectively 12 fold and 2–3 fold times increased risk of developing late-stage AD than

APOE2 or 3 carriers (Belloy et al., 2019). Depending on the ethnicity, 10–25% of the population is carrier of APOE4, which makes it the most prevalent genetic risk factor for AD. APOE4 has been clearly linked to brain hypometabolism, which was shown to precede neurodegeneration by years in APOE4(+) patients (Farrer et al., 1997; Raber et al., 2004; Reiman et al., 2004). APOE is a major cholesterol carrier involved in lipid metabolism. In the brain, APOE is primarily produced by astrocytes and regulates lipids delivery to neurons that are necessary for their structural maintenance, as well as injury repair (Xu et al., 1996, 2006; Mahley and Rall, 2000; Bu, 2009). In conditions of stress or injury, APOE can also be expressed by neurons (Mahley et al., 2006). Several studies have shown strong association between APOE4, metabolic genes expression and cerebral glucose uptake in human brains (Jagust et al., 2012; Carbonell et al., 2016; Wu et al., 2018). Mouse models carrying the APOE4 human allele also have reduced metabolic gene expression and cerebral glucose uptake compared to APOE3 expressing models (Alata et al., 2015; Lin et al., 2017; Williams et al., 2020). At the cellular level, APOE4-expressing astrocytes exhibit altered glycolysis, glucose uptake and lactate secretion (Wu et al., 2018; Williams et al., 2020). Interestingly, lactate transferred from astrocytes to neurons is used for the synthesis of lipid droplets in neurons, which in turn are transported back to astrocytes through carriers that include fatty acid transport proteins (FATPs) and apolipoproteins neurodegeneration (Liu et al., 2017). Expression of APOE4 impairs this transport of lipid droplets between neurons and astrocytes, which in turn promotes neurodegeneration (Liu et al., 2017).

Brain insulin resistance is also believed to contribute to metabolic dysfunctions in AD (Rivera et al., 2005). Thus, a growing body of epidemiological and molecular evidence indicates an overlap in risk, comorbidity, and pathophysiological mechanisms across Type 2 diabetes (T2D), mild cognitive impairment (MCI), AD and other types of dementia such as vascular dementia, Lewy body dementia (LBD) and FTD (Arnold et al., 2018). Studies also indicate that T2D patients are at increased risk of developing MCI or AD (Arnold et al., 2018). While insulin resistance is a central feature of T2D, research from the past few years has also shown that it is present in the brains of patients with dementia, even in the absence of T2D (De Felice et al., 2009; Zhao and Townsend, 2009; El Khoury et al., 2014). Moreover, cerebral levels of insulin and insulin receptor (IR) are lower in the brain of AD patients, and evidence for insulin signaling impairment in post-mortem brain tissue of AD patients and in animal models of AD has been shown (Steen et al., 2005; Chiu et al., 2008; Talbot et al., 2012). Insulin and insulin-like growth factors (IGFs) regulate key neuronal functions such as survival, energy metabolism and synaptic plasticity (Hoyer, 2002). Interestingly, insulin-mediated signaling pathways are impacted by APOE4 through the reduction of the expression of insulin receptor substrate 1 (IRS1) and Akt pathway in both mouse models and human brain tissue (Ong et al., 2014; Keeney et al., 2015), and the sequestration of IR in endosomes in an age-dependent manner (Zhao et al., 2017).

Human and animal studies have shown that dysregulation of insulin function contributes to aging and to the development of neurodegenerative diseases (Craft and Watson, 2004). In this context, impaired glucose utilization, mitochondrial dysfunction, reduced ATP production, and energy shortage in AD led to the hypothesis that these abnormalities could be mediated, at least in part, by desensitization of IR in the brain (Hoyer, 2002; Craft and Watson, 2004; de la Monte, 2009). Several preclinical studies have highlighted the impact of insulin dysregulation in models of cognition. In mice, intracerebroventricular injection of streptozotocin was found to reduce brain glucose metabolism, mitochondrial function, IR activity and spatial learning and memory (Duelli et al., 1994; Hoyer et al., 2000; de la Monte and Wands, 2006). Experimental induction of brain insulin resistance and insulin deficiency in mice causes AD-like neurodegeneration and cognitive impairment (Lester-Coll et al., 2006). In the brain, both neurons and astrocytes are impacted by insulin signaling. In neurons, insulin signaling modulates the expression of GABA, NMDA and AMPA receptors, catecholamine release, and glucose uptake via GLUT3. In astrocytes, insulin enhances glycogen storage, stimulates glucose uptake via GLUT1 and modulates inflammatory response (Heni et al., 2011; Arnold et al., 2018). Interestingly, activation of insulin-mediated pathways was downregulated in astrocytes in response to elevated chronic insulin levels, but not in neurons (Clarke et al., 1984). These cellular differences could have implications in the effects of T2D and insulin resistance on the function of different brain cell types.

In AD brains, reactive astrocytes are preferentially located in the vicinity of amyloid plaques, where they exhibit abnormal morphology (Rodriguez et al., 2009; Acosta et al., 2017; Liddelow et al., 2017). In the early stage of the disease, activated astrocytes have neuroprotective action by internalizing and degrading amyloid plaques, while upon progression of the disease, deposit of amyloid plaques leads to astrocytic death that in turn contribute to further development of the pathology (Nagele et al., 2004). Regarding the consequences of hypometabolic state in the brain, a study showed that amyloid plaques impair glucose uptake by interfering with exocytosis-dependent GLUT3 membrane expression (Uemura and Greenlee, 2001; Prapong et al., 2002). Several reports have described some adaptations of the astrocytic metabolism to amyloid plaques *in vitro*, with alterations of glycolysis and mitochondrial activity (Allaman et al., 2010; Oksanen et al., 2017; van Gijsel-Bonnello et al., 2017; Carter et al., 2019) and the activation of several intracellular cascades leading to inflammation, oxidative stress and calcium dysregulation (De Strooper and Karran, 2016).

CURRENT THERAPEUTIC STRATEGIES TO TARGET BRAIN HYPOMETABOLISM

Insulin Signaling

Considering the hypometabolic state and the emerging consideration of insulin signaling in AD, a number of therapeutic strategies targeting insulin-mediated pathways have been considered in order to restore brain energy metabolism (Kellar and Craft, 2020). These approaches include the use of insulin sensitizer agents or intranasal insulin to restore insulin signaling

in AD, as well as antidiabetic drugs such as Metformin and Glucagon-like peptide-1 receptor (GLP-1R) agonists.

First, intranasal insulin has been developed with the objective to efficiently deliver insulin directly into the brain without changing peripheral levels that could cause insulin resistance (Born et al., 2002). Insulin has been known for many years to positively modulate brain glucose utilization (Havrankova et al., 1978; Bingham et al., 2002; Taouis and Torres-Aleman, 2019). In animal models of AD, intranasal insulin was found to reduce cerebral oxidative stress, tau phosphorylation and amyloid load, and improves cognitive functions (Barone et al., 2019) (see **Table 1**). In humans, intranasal insulin has shown promising clinical data in MCI and AD (Kellar and Craft, 2020)

(see **Table 2**). For instance, a pilot trial reported improvement of cognition in healthy volunteers after intranasal insulin administration (Benedict et al., 2004, 2007). A subsequent study confirmed positive effect of intranasal insulin in patients with MCI or mild AD (Reger et al., 2008a,b). Further study on over 100 patients with MCI or mild to moderate AD reported some preservation of cognition and function, and higher cerebral glucose utilization assessed by FDG PET, although no changes were observed in AD biomarkers (Craft et al., 2012; Claxton et al., 2013). These results led to the establishment of a larger Phase 2 and 3 studies that have enrolled nearly 300 people with MCI or early-stage AD. In this trial, treatment with intranasal insulin showed positive impact on primary outcome ADAS-Cog12

TABLE 1 | Preclinical evidence of compounds targeting brain energy metabolism.

Treatment	Model	Results	References
Insulin signaling			
Insulin	Human primary astrocytes	↑ Glucose uptake and glycogen storage in astrocytes	Heni et al., 2011; Arnold et al., 2018
Insulin (intranasal)	Aged APP/PS1/Tau (3Tg) AD mouse models	↑ Cognition; ↓ Cerebral oxidative stress, tau phosphorylation, Aβ load	Barone et al., 2019
GLP1-R agonists			
Liraglutide	APP/PS1, 3Tg, Aβ$_{1-42}$ ICV injections AD mouse model	↑ Neuronal survival, synaptic function, learning and memory ↓ Neuroinflammation, amyloid plaque, hyperphosphorylated Tau	McClean et al., 2011, 2015; Hansen et al., 2016a,b; Qi et al., 2016; Chen et al., 2017
Liraglutide	Aβ cortical injection in non-human primate	↑ Insulin signaling, synapse number; ↓ Neuroinflammation	Lourenco et al., 2013; Batista et al., 2018
Liraglutide	5 × FAD AD mouse model	Restored defective metabolism of astrocytes (incl. lactate release); ↑ Neuroprotection through enhanced astrocytic glycolysis; ↑Cognition	Zheng et al., 2021
Liraglutide	Rodent models of PD, stroke and TBI	↑ Neuroprotection and behavioral activity in mouse and rat models of PD; ↑ Brain repair after cerebral ischemic injury; ↑ Cognition; ↓ neurodegeneration and neuroinflammation in mouse and rat models of TBI	Liu et al., 2015; Hansen et al., 2016b; Badawi et al., 2017; Bader et al., 2019; He et al., 2020
Exendin-4	3Tg AD + STZ-induced-T2D mouse model	↑ Plasma insulin levels; ↑ Aβ brain levels	Li et al., 2010
Exendin-4	Mouse and rat models of PD and TBI	↑ Neuroprotection, adult neurogenesis, behavioral activity	Perry and Greig, 2005; Perry et al., 2007; Bertilsson et al., 2008; Harkavyi et al., 2008; Li et al., 2009; Eakin et al., 2013; Rachmany et al., 2013
Metformin			
Metformin	Primary rat astrocytes	↑ Glycolysis and lactate production by astrocytes	Westhaus et al., 2017
Metformin	High fat diet in mice and rats	↑ Mitochondrial function, neuroprotection, cognition, autophagy in mouse models. One study showed no effect on cognition in rats (McNeilly et al., 2012)	McNeilly et al., 2012; Pintana et al., 2012; Lennox et al., 2014; Allard et al., 2016; Chen et al., 2021
Ketogenic diet			
KD	Rat	↑ Brain GLUT1 and MCT1 levels	Leino et al., 2001
KD	Mouse	↑ Brain mitochondrial function, ATP levels, oxidative stress resistance	Sullivan et al., 2004
KD, ketone ester	APP, APP/PS1, 3Tg AD mouse models	↑ Glycolysis, mitochondrial functions, cognition, motor performance ↓ Anxiety, Aβ levels, hyperphosphorylated Tau	Van der Auwera et al., 2005; Beckett et al., 2013; Kashiwaya et al., 2013; Zhang et al., 2013; Pawlosky et al., 2017
β-HB	MPTM-induced mouse model of PD	↑ Mitochondrial function, motor performance	Tieu et al., 2003
Caprylic triglyceride	SOD1-G93A mouse model of ALS	↑ Neuroprotection, motor performance	Zhao et al., 2012

3Tg, triple transgenic; PS1, presenilin 1; Aβ, Amyloid β; AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; APP, amyloid precursor protein; β-HB, β-hydroxybutyrate; GLUT1, glucose transporter 1; ICV, intracerebroventricular; GLP-1R, Glucagon-like peptide-1 receptor; KD, ketogenic diet; MCT1, monocarboxylate transporter 1; PD, Parkinson's disease; STZ, Streptozotocin; T2D, Type 2 Diabetes.

TABLE 2 | Clinical evidence of compounds targeting brain energy metabolism in neurodegenerative diseases.

Treatment	Indication	Study design	Results	References
Insulin				
Intranasal insulin	Healthy	Intranasal insulin (4 × 40 IU/d) vs. placebo; 8 weeks; 38 subjects	↑ Declarative memory (delayed recall of words) and mood; No changes in blood glucose and plasma insulin	Benedict et al., 2004
Intranasal insulin or ASP-I	Healthy	Acute/8 weeks intranasal insulin or ASP-I (rapid acting insulin analog) (4 × 40IU/day) vs. placebo; 36 male subjects	↑ Declarative memory (word lists) after long-term administration (ASP-I > insulin); No change in blood glucose and plasma insulin	Benedict et al., 2007
Intranasal insulin	MCI or AD	Acute intranasal insulin (10, 20, 40 or 60 IU) vs. placebo; 33 patients	↑ Verbal memory in APOE4 (–) patients (max at 20 IU) ↓ Verbal memory in APOE4 (+) patients (n.s.); No change in blood insulin and glucose levels	Reger et al., 2008a
Intranasal insulin	Early AD	Intranasal insulin (20 IU BID) vs. placebo; 21 days; 24 patients	↑ Verbal information retention after delay, attention, functional status; ↑ Aβ40/42 ratio; No change in blood insulin and glucose levels	Reger et al., 2008b
Intranasal insulin	MCI or mild to moderate AD	Intranasal insulin (20, 40 IU) vs. placebo; 4 months; 104 patients	↑ Memory (delayed story) (ADAS-Cog and ADCS-ADL in younger participants); ↓ Dementia Severity Rating Scale; ↓ CMRGlc decline (FDG PET in precuneus, frontal and occipital cortices)	Craft et al., 2012
Intranasal insulin	MCI or AD	Intranasal insulin (20, 40 IU) vs. placebo; 4 months; 104 subjects	↑ Memory (delayed story; dose and sex-dependent); No change in memory in APOE4 (+) subjects	Claxton et al., 2013
Intranasal insulin or detemir	MCI or mild to moderate AD	Intranasal insulin, insulin analog detemir or placebo; 4 months; 36 patients	↑ Memory composite (delayed list and story recall) and preserved brain volume after insulin (not detemir); ↓ CSF Tau-P181/Aβ42 after insulin (not detemir); No change in daily functioning (insulin or detemir)	Craft et al., 2017
Intranasal insulin	PD	Intranasal insulin (40 IU) vs. placebo; 4 weeks; 16 patients	↑ Cognition (verbal fluency) and motor function	Novak et al., 2019
Intranasal insulin	MCI or AD	Intranasal insulin (40 IU) vs. placebo; 12 months (followed by 6 months open label extension); 289 patients	No change in memory (ADAS-Cog-12) (differences between groups depending on the injection device used); No change in CSF AD biomarkers, CSF insulin or blood glucose	Craft et al., 2020
Intranasal glulisine	MCI or mild AD	Intranasal Glulisine (rapid-acting insulin analog) (20 IU BID) vs. placebo; 6 months; 35 patients	No change in cognition (ADAS-Cog13), CDR global score, FAQ or mood. No change in blood glucose or insulin levels	Rosenbloom et al., 2021
GLP1-R agonists				
Liraglutide	AD	Liraglutide vs. placebo; 6 months; 38 patients	↓ CMRGlc decline (FDG PET in precuneus, cerebellum, temporal and occipital cortices); No change in cognition or Aβ (global and regional brain areas)	Egefjord et al., 2012; Gejl et al., 2016
Liraglutide	MCI	Liraglutide vs. placebo; 12 weeks; 41 patients	↑ Connectivity in the DMN (fMRI); No change in cognition	Watson et al., 2019
Liraglutide	Mild AD	Liraglutide vs. placebo; 1 year; 204 patients (without T2D)	↑ Memory (composite z-score); ↑ Temporal lobe and total gray matter volumes; No change in CMRGlc (FDG PET)	Femminella et al., 2019
Liraglutide	T2D	Liraglutide vs. placebo; 3 weeks; 40 patients (obesity with pre-diabetes or early-stage T2D)	↑ Memory (composite z-score: attention, memory, executive control)	Vadini et al., 2020
Semaglutide	MCI or mild AD	Semaglutide vs. placebo; 2 years; 2 studies of 1840 patients	Estimated study completion date: 2025	Clinical trials NCT04777396 and NCT04777409
Metformin				
Metformin	AD	Long-term use of Metformin on 7'686 patients aged 65+	↑ Risk of developing AD with long-term use of Metformin (presumably through Vit B12 deficiency)	Imfeld et al., 2012
Metformin	MCI	Metformin vs. placebo; 1 year; 80 patients (overweight and non-diabetic)	↑ Memory on SRT; No change in ADAS-Cog, glucose uptake or plasma Aβ	Luchsinger et al., 2016
Metformin	MCI or AD	Metformin vs. placebo; 8 weeks; 20 patients (non-diabetic)	↑ Executive functions; ↑ Learning and memory (n.s.); No change in AD biomarkers	Koenig et al., 2017
Metformin	AD	Meta analyses	↓ Dementia incidence in diabetic patients treated with Metformin	Campbell et al., 2018; Chin-Hsiao, 2019; Samaras et al., 2020; Sluggett et al., 2020

(Continued)

TABLE 2 | (Continued)

Treatment	Indication	Study design	Results	References
Metformin	MCI	Metformin vs. placebo; 2 years; 370 patients (overweight/obese w/o T2D)	Estimated study completion: 2025	Clinical trial NCT04098666
Ketogenic Diet				
MCT	Mild to moderate AD	MCT (Ketasyn/AC-1202) vs. placebo; 12 weeks; 152 patients	↑ Memory (ADAS-Cog) in APOE4(–), but not in APOE4(+) subjects	Henderson et al., 2009; Henderson and Poirier, 2011
KD	MCI	Low carbohydrates (5–10% cal.) vs. high carbohydrate (50% cal.) diet; 6 weeks; 23 patients	↑ Memory, positively correlated with ketone levels	Krikorian et al., 2012
MAD	MCI or early-stage AD	MAD vs. recommended diet; 12 weeks; 27 patients	↑ Episodic memory (n.s.); Low adherence	Brandt et al., 2019
KD	MCI in PD	KD vs. recommended diet; 8 weeks; 14 patients	↑ Memory, positively correlated with body weight loss; No effect on motor function	Krikorian et al., 2019
MCT	MCI	MCT (kMCT drink) vs. placebo drink; 6 months; 52 patients	↑ Cognitive functions	Fortier et al., 2019
MCT	Mild to moderate AD APOE4(–)	MCT (jelly) vs. placebo; 30 days; 46 patients	↑ Memory (ADAS-Cog)	Xu et al., 2020
MCT	Mild to moderate AD APOE4 (–)	MCT (Tricaprilin/AC-1204) vs. placebo; 26 weeks; 413 patients	No effect on memory (ADAS-Cog11)	Henderson et al., 2020
MCT	MCI	MCT (kMCT drink) vs. placebo drink; 6 months; 122 patients	↑ Cognitive functions	Fortier et al., 2021
MCT	Mild to moderate AD APOE4 (–)	MCT (AC-SD-03/CER-0001) vs. placebo; 26 weeks; 300 patients with decreased FDG PET signal	Estimated study completion: 2024	Clinical trial NCT04187547

ADAS-Cog, The Alzheimer's Disease Assessment Scale–Cognitive Subscale; AD, Alzheimer's disease; ADCS-ADL, Alzheimer's disease cooperative study – Activity of daily living; ALS, Amyotrophic lateral sclerosis; APOE4, apolipoprotein 4; BID, twice a day; CMRGlc, cerebral metabolic rate of glucose; CDR, clinical dementia rating; CSF, cerebrospinal fluid; DMN, default mode network; FAQ, Functional Activities Questionnaire; FDG-PET, fluorodeoxyglucose-positron emission tomography; IU, international units; KD, ketogenic diet; MAD, Modified Atkins Diet; MCI, mild cognitive impairment; MCT, Medium Chain Triglyceride; n.s., not significant; PD, Parkinson's disease; SRT, Selective Reminding Test; T2D, Type 2 Diabetes.

memory assessment at 12 and 18 months in a patient's cohort that has used one of the two devices used for insulin delivery, while another patient's cohort that has used another delivery device failed to benefit from the treatment (Craft et al., 2020). Other series of clinical studies have evaluated long-acting insulin analog Detemir and showed that treatment of 50 MCI or AD patients led to memory improvement in APOE4 carriers, but worsened memory in non-carriers (Claxton et al., 2013). Another study showed that insulin, but not long-acting analog Detemir, increased memory and preserved volume in several brain regions (Craft et al., 2017). A small trial examining the effect of the rapid acting insulin analog Glulisine in patients with MCI or middle-stage AD failed to show any acute impact in cognition (Rosenbloom et al., 2021). Nasal insulin has also been tested in other neurodegenerative diseases, showing for example improved clinical outcome in PD severity (Novak et al., 2019).

Glucagon-Like Peptide-1 Receptor Agonists

Another therapeutic strategy aiming at restoring brain metabolism by targeting insulin-related pathway is the use of Glucagon-Like Peptide-1 Receptor (GLP-1R) agonists. GLP-1 is an incretin hormone derived from proglucagon and secreted by the small intestine in response to food intake. GLP-1R is expressed in pancreatic β-cells, kidney, heart, and CNS (Yildirim Simsir et al., 2018). Activation of GLP-1R leads to insulin release by β-cells, which in turn stimulates glucose uptake. While GLP-1 is well known for its action in the regulation of peripheral metabolism, it was also shown to play key roles in CNS functions. For instance, GLP-1 is secreted by neurons in the nucleus tractus solitarius (NTS), which results in anorexic effect and transmit vagal motor information to the pancreas (Yildirim Simsir et al., 2018). Other studies showed that overexpression of GLP-1R in the rat hippocampus improves learning, memory and neuroprotection (During et al., 2003), while transgenic mice lacking GLP-1R have deficits in learning, synaptic plasticity and cognition (Abbas et al., 2009). Interestingly, effects of GLP-1 on energy balance were found to be mediated by astrocytes (Reiner et al., 2016). Thus, large number of astrocytes in the NTS respond to GLP-1R agonists by intracellular calcium and cAMP signaling, while blocking NTS astrocytes activity attenuated GLP-1R agonist effects on food intake in rats (Reiner et al., 2016). These data suggest that astrocytes play a role in the effects of GLP-1 in the brain (Cui et al., 2021).

Preclinical and clinical evidence indicate therapeutic potential for some of the GLP-1R agonists that are commonly used for the treatment of diabetes and obesity (Yildirim Simsir et al., 2018)

(see **Tables 1**, **2**, respectively). They include Liraglutide (Novo Nordisk), Semaglutide (Novo Nordisk) and Exendin-4, also known as Exenatide (AstraZeneca). First, in rodent models of AD, the GLP-1 analog Liraglutide was shown to promote neuronal survival, increase synaptic function, reduce neuroinflammation, amyloid plaque and hyperphosphorylated Tau, and support learning and memory (McClean et al., 2011, 2015; Hansen et al., 2016a; Qi et al., 2016; Chen et al., 2017; Holscher, 2018). In non-human primates, Liraglutide improved insulin signaling, reduced inflammation and restored synapse number that were caused by the cortical injections of β amyloid (Lourenco et al., 2013; Batista et al., 2018). Interestingly, a recent study using mouse model of AD showed that Liraglutide has a specific impact on astrocytes (Zheng et al., 2021). Treatment of AD mouse-derived astrocytes with Liraglutide resulted in a neuroprotective action and restored defective metabolic pathways, including lactate secretion (Zheng et al., 2021). Liraglutide also showed positive effects in preclinical models of other neurological diseases, including PD (Liu et al., 2015; Hansen et al., 2016b; Badawi et al., 2017), stroke (He et al., 2020) and TBI (Bader et al., 2019). The other GLP-1R agonist Exendin-4 also exhibited neuroprotective effects in a mouse model of AD (Li et al., 2010) and PD (Perry and Greig, 2005; Perry et al., 2007; Bertilsson et al., 2008; Harkavyi et al., 2008; Li et al., 2009; Eakin et al., 2013; Rachmany et al., 2013).

In humans, a pilot study has first tested the effects of 6-month Liraglutide treatment in 38 patients with AD (Egefjord et al., 2012). Liraglutide led to a clear increase in brain glucose utilization, as revealed by FDG PET (Femminella and Edison, 2014; Gejl et al., 2016). Another pilot trial was done with Liraglutide on 41 middle- to late-aged individuals with elevated blood glucose or diabetes and cognitive complaints. Primary outcome, which included fMRI before and after treatment, revealed improved connectivity within the default mode network (DMN), a system that is defective in AD (Watson et al., 2019). A study in 40 obese subjects with pre-diabetes or newly diagnosed T2D treated for 3 weeks with Liraglutide indicated an increase in short term memory (Vadini et al., 2020). Most recent Phase IIb study (ELAD study) on 204 patients with mild AD and no diabetes failed to see benefit of Liraglutide on primary outcome of FDG PET, but revealed improved in cognition, as well as temporal lobe and total brain gray matter volumes (Femminella et al., 2019). Semaglutide, another GLP-1R agonist, is set to be tested in two large Phase 3 studies (EVOKE and EVOKE Plus; NCT04777396 and NCT04777409). These trials each plan to enroll 1'840 patients with MCI or middle-stage dementia for a duration of 2 years. The clinical protocol is based on the *post hoc* data analyses from three clinical studies on T2D showing a 53% reduced risk of developing dementia in people who received Semaglutide or Liraglutide. Liraglutide, Semaglutide and Exendin-4 are also all currently being tested in clinical studies for PD.

Metformin

Repositioning of Metformin, one of the most used medication for the treatment of T2D, has been another strategy to improve brain energy deficits in neurodegenerative diseases. Metformin acts through the activation of AMPK, an important regulator of glucose homeostasis. Activation of AMPK decreases gluconeogenesis, lowers blood glucose and restores insulin sensitivity. Metformin has been shown to reduce inflammation and oxidative stress, and to promote neurogenesis (Wang et al., 2012; Rotermund et al., 2018; Bharath et al., 2020). Interestingly, pleiotropic effects of Metformin have been hypothesized to be mediated, at least in part, by the increased circulating concentrations of lactate produced by AMPK-mediated glucose uptake, and its use as a direct energy source in various organs (Giaccari et al., 2021). In this context, Metformin was found to directly enhance glycolysis and production of lactate by astrocytes in the brain (Westhaus et al., 2017). Metformin was found to have positive impact in cognition in high fat diet mouse models (Pintana et al., 2012; Lennox et al., 2014; Allard et al., 2016), but others found no effect of Metformin in a rat model of high fat diet-induced cognitive deficit (McNeilly et al., 2012). In a mouse model of AD, Metformin attenuated Tau aggregates and amyloid load by ameliorating microglial autophagy (Chen et al., 2021) (**Table 1**). Interestingly, Metformin was found to repress the expression of Thioredoxin-interacting protein (Txnip), an inhibitor of Thioredoxin, through AMPK-mediated pathway (Chai et al., 2012). Repression of Txnip, which has been shown to improve glucose utilization and uptake (Parikh et al., 2007), is postulated to participate, at least in part, in the effects of Metformin on glucose metabolism.

In humans, several clinical studies have been assessing the impact of Metformin in MCI and AD (**Table 2**). First, a pilot study in 80 overweight non-diabetic people with MCI indicated that administration of Metformin for a duration of 1 year led to better performance on the Selective Reminding Test (SRT) of memory, but did not change other outcomes including ADAs-Cog, glucose uptake and plasma amyloid levels (Luchsinger et al., 2016). A smaller trial in 20 non-diabetic people with MCI or AD showed that Metformin improved executive functions, led to a trend toward better learning and memory, but did not change AD biomarkers (Koenig et al., 2017). However, contrasting study showed that long-term use of Metformin could also increase the risk of developing AD, presumably through its effect on Vitamin B12 deficiency, which is a cause of dementia (Imfeld et al., 2012). A multicentric Phase 2/3 trial that investigates the effect of Metformin on memory of 370 overweight or obese people with MCI is currently ongoing (NCT04098666). Interestingly, clinical meta-analyses showed that cognitive impairment, as well as dementia incidence, were significantly reduced in diabetic patients that were treated with Metformin (Campbell et al., 2018; Chin-Hsiao, 2019; Samaras et al., 2020; Sluggett et al., 2020).

Ketogenic Diet

Ketogenesis is a physiological mechanism whereby ketone bodies (acetoacetate, β-hydroxybutyrate and acetone) are produced by the liver in response to fasting, exercise or reduced carbohydrate availability (Puchalska and Crawford, 2017). Ketone bodies that are released in the circulation can be used by extra-hepatic tissues as alternative energy sources. In the mitochondria of energy-consuming cells, ketone bodies are converted in acetyl-CoA

and incorporated in the TCA cycle. The brain can adapt to the utilization of ketone bodies for up to 70% of its energy requirements (Veech, 2004). In humans, the classical ketogenic diet (KD) consists in a 4 to 1 ratio of fats to proteins and carbohydrates, which physiologically mimics the fasting state and leads to hepatic ketogenesis. Although safe and efficiently enhancing levels of circulating ketone bodies, KD usually lacks long-term adherence. Alternative diets consist in the less strict Modified Atkins Diet (MAD) or supplementation to the normal diet with exogenous ketogenic agents such as medium-chain triglycerides (MCTs).

Ketogenic diet is commonly used for the treatment of refractory epilepsy (D'Andrea Meira et al., 2019), and has been proposed as a therapeutic strategy to restore energy deficit in neuropathologies with metabolic dysfunction. Interestingly, transport of ketone bodies is directly affected by ketogenic diet through the upregulation of MCT1 and GLUT1 in the brain (Leino et al., 2001). Preclinical evidence showed promising results for the neuroprotective properties of KD (Paoli et al., 2014) (**Table 1**). For instance, KD in mice improved mitochondrial function, decreased oxidative stress, and increased ATP cerebral concentrations (Sullivan et al., 2004). In several transgenic mouse models of AD, KD was found to improve glycolysis,

mitochondrial function and cognition, while reducing oxidative stress and amyloid deposition (Van der Auwera et al., 2005; Beckett et al., 2013; Kashiwaya et al., 2013; Zhang et al., 2013; Pawlosky et al., 2017). KD also improved metabolism, mitochondrial activity and motor functions in mouse models of PD (Tieu et al., 2003) and ALS (Zhao et al., 2012).

In humans, the impact of KD in neurodegenerative diseases has been tested in different clinical settings (Dewsbury et al., 2021) (**Table 2**). First, pilot study showed that 12-week KD in MCI or early-stage AD patients led to non-significant trend of memory improvement (Brandt et al., 2019). In a group of 23 patients with MCI, low carbohydrate diet was found to improve learning and memory performance compared to high carbohydrate diet (Krikorian et al., 2012). In a pilot study on 14 participants with MCI in PD, 8-week long KD enhanced cognitive performance (Krikorian et al., 2019). A larger multicentric study with 152 AD patients showed that 12-week-long administration of MCT Ketasyn/AC-1202 (Cerecin), improved memory performance in APOE4(−), but not in APOE4(+) patients (Henderson et al., 2009; Henderson and Poirier, 2011). Another pilot study showed that treatment with MCTs in APOE4(−) AD patients for 30 days improved memory performance (Xu et al., 2020). However, no significant differences
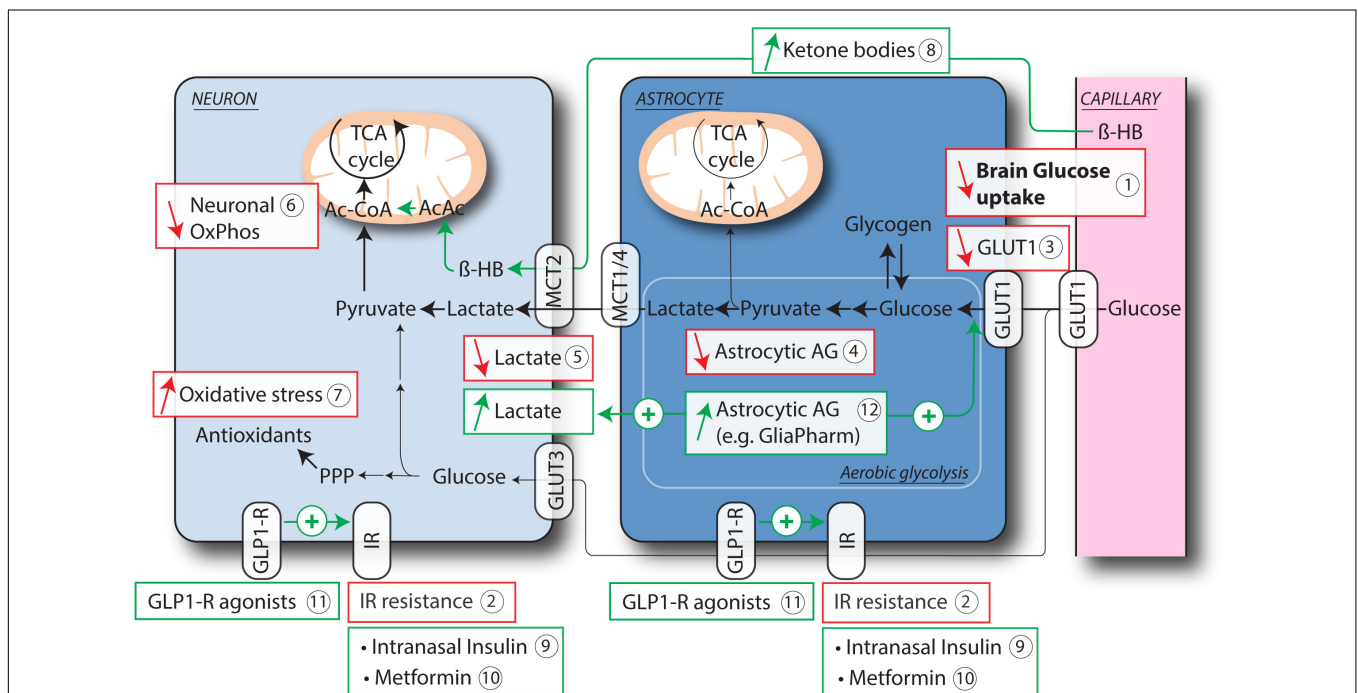

FIGURE 1 | Age-related astrocytic and neuronal deficits leading to brain hypometabolism and current therapeutic strategies. Brain glucose hypometabolism is a hallmark of aging and neurodegeneration, as shown in particular by FDG PET studies (1). Resistance to Insulin has been proposed to account, at least in part, for this hypometabolism (2). Astrocytes and neurons both express insulin receptor (IR). Other key features of brain hypometabolism include reduced expression of GLUT1 on astrocytes and endothelial cells (3), decreased aerobic glycolysis (AG) in astrocytes (4) and consequent impaired release of lactate (5), reduced mitochondrial activity in neurons (6) and increased oxidative stress (7). Therapeutic strategies that aim at restoring brain energy metabolism include the use of ketone bodies as alternative energy source for neuronal mitochondrial OxPhos, either through ketogenic diet or medium chain triglycerides (8), targeting IR resistance either directly with intranasal Insulin (9) or Metformin (10), or via activation of GLP-1R (11). Another specific therapeutic approach consists in improving astrocytic AG (12), which results in increased glucose uptake and lactate release by astrocytes. Ac-CoA, acetyl-CoA; AcAc, acetoacetate; β-HB, β-hydroxybutyrate; GLP1-R, glucagon-like peptide 1 receptor; GLUT1, 3, glucose transporter 1, 3; IR, insulin receptor; MCT1, 2, 4, monocarboxylate transporter 1, 2, 4; OxPhos, oxidative phosphorylation; PPP, pentose phosphate pathway; TCA cycle, tricarboxylic acid cycle.

were observed in subsequent trial on 413 AD patients after 26-week long intervention with MCT Tricaprilin/AC-1204 (Cerecin) (Henderson et al., 2020). Despite these contrasting results, Phase 3 trial with Cerecin's MCT AC-SD-03/CER-0001 has been registered and plans to enroll 300 people with mild to moderate AD that exhibit decreased FDG PET signal and have APOE4(−) genotype (NCT04187547). Finally, a clinical study that assessed the metabolic effect of MCT-based regimen kMCT-ONS (Nestlé Health Science) in 52 people with MCI reported increase in plasma and brain ketones, while brain glucose uptake did not differ (Fortier et al., 2019). A larger 6-month trial in 122 MCI patients showed that treatment with kMCT-ONS diet led to improvements in memory tests, executive function and language (Fortier et al., 2021).

CONCLUSION

Brain hypometabolism is one of the first homeostatic dysregulation that occurs in age-related neurodegenerative diseases. Aging, APOE4 and insulin resistance are among the key factors that lead to brain hypometabolism. Hypometabolic changes are characterized by decreases in brain glucose uptake, expression of glucose transporters, astrocytic aerobic glycolysis, lactate release, neuronal mitochondrial function and increased oxidative stress (**Figure 1**). This homeostatic imbalance results in an energy gap, which renders neurons more vulnerable to a variety of insults and also decreases network connectivity (de la Torre, 2008). While brain hypometabolism occurs in physiological aging, it represents a significant contributing factor to a number of neurodegenerative diseases such as AD (Thomas et al., 2015; Butterfield and Halliwell, 2019), ALS (Lee et al., 2012; Vandoorne et al., 2018), depression (Rajkowska and Stockmeier, 2013), multiple sclerosis (Saab et al., 2016), migraine (Gross et al., 2019), epilepsy (de Melo et al., 2021), TBI (Carteron et al., 2018), retinal degeneration (Ait-Ali et al., 2015), stroke

(Berthet et al., 2012), or spinal cord injury (SCI) (Babetto et al., 2020; Li et al., 2020).

To target brain hypometabolism, several different therapeutic approaches that have shown promising results are presented in this review. For instance, intranasal insulin, which increases brain glucose uptake, was shown to improve cognition in AD and MCI patients. GLP-1R agonists and Metformin also improved glucose utilization and cognitive function in AD mouse models and patients. Ketogenic diet, another therapeutic strategy that aims at providing alternative source of energy to neurons, improves metabolic functions and cognition in preclinical models and human AD and MCI patients. These approaches have shown promising results, but lack selectivity to brain pathways. More targeted metabolic approaches constitute future avenues of development to tackle hypometabolic neurological diseases. Among these innovative approaches, our strategy at GliaPharm aims at specifically improving aerobic glycolysis in astrocytes, which results in the activation of the ANLS, increase in brain glucose uptake and release of lactate that is used by neurons as preferential energy source. This approach led to promising results in the impact on brain energy metabolism and neuroprotection *in vitro* and in different preclinical models.

The increasing amount of evidence linking brain aging, neurological diseases and hypometabolism has therefore opened avenue for innovative therapeutic strategies, either through non-specific drug repurposing or targeted approaches to improve brain metabolism. These approaches could have disease-modifying impact in the management of the brain energy crisis in a number of neurological diseases.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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