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Do microglia metabolize fructose in Alzheimer's disease?

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Abstract

Alzheimer's disease (AD) is an age-associated neurodegenerative disorder with a complex etiology. While emerging AD therapeutics can slow cognitive decline, they may worsen dementia in certain groups of individuals. Therefore, alternative treatments are much needed. Microglia, the brain resident macrophages, have the potential to be novel therapeutic targets as they regulate many facets of AD, including lipid droplet (LD) accumulation, amyloid beta (Aβ) clearance, and neuroinflammation. To carry out such functions, microglia undergo phenotypic changes, which are linked to shifts in metabolism and substrate utilization. While homeostatic microglia are driven by oxidative phosphorylation (OXPHOS) and glycolysis, in aging and AD, microglia shift further towards glycolysis. Interestingly, this "metabolic reprogramming" may be linked to an increase in fructose metabolism. In the brain, microglia predominantly express the fructose transporter *SLC2A5* (GLUT5), and enzymes involved in fructolysis and endogenous fructose production, with their expression being upregulated in aging and disease. Here, we review evidence for fructose uptake, breakdown, and production in microglia. We also evaluate emerging literature targeting fructose metabolism in the brain and periphery to assess its ability to modulate microglial function in AD. The ability of microglia to transport and utilize fructose, coupled with the well-established role of fructose in metabolic dysfunction, supports the notion that microglial fructose metabolism may be a novel potential therapeutic target for AD.

Keywords Fructose, Microglia, Immunometabolism, Neurodegeneration, Metabolic reprogramming

Introduction

Alzheimer's disease (AD) is an age-associated and multifaceted neurodegenerative disorder characterized by protein aggregates (i.e., amyloid beta (Aβ), tau [1]), lipid droplet (LD) accumulation [2], neuroinflammation [3], and neurodegeneration [4]. It is estimated that 6.9 million Americans aged 65 and older are living with AD and Alzheimer's-related dementia in 2024 [5]. While recent FDA-approved therapies may slow disease progression [6–8], they only target one aspect of the disease (e.g., Aβ), are associated with major side effects, and are less effective in individuals with advanced disease or who carry the main AD risk gene, apolipoprotein E4 (*APOE4*) [6, 9]. Therefore, alternative therapeutics that target AD more broadly are much needed. Since microglia, the brain's resident macrophages, regulate many aspects of AD neuropathogenesis, such as Aβ phagocytosis [10], tau spreading [11], inflammation [12], and lipid homeostasis [13, 14], targeting microglia holds enormous potential for developing new strategies with a wider impact on AD. In the pursuit of ways to modulate microglial function to improve AD outcomes, there has been a renewed interest in the concept of "immunometabolism"; the notion that metabolic shifts can influence the immune response

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[15]. Microglia commonly undergo immunometabolic shifts when rapidly responding to changes in the microenvironment. In response to specific stimuli, microglia adopt a variety of phenotypic states uniquely tailored to a functional outcome, such as phagocytosis [16], cytokine release [17], and antigen presentation [18]. During phenotypic transitions, and to cope with increased energy demands, microglia rapidly increase glycolysis and reduce mitochondrial oxidative phosphorylation (OXPHOS) [19–23]. Although this "metabolic reprogramming" is initially adaptive, chronic reprogramming eventually leads to elevated fructose metabolism, proinflammatory cytokine production, LD accumulation, and impaired phagocytosis, all hallmarks of microglial dysfunction and AD neuropathogenesis [19–21, 24].

Emerging pathways that may drive the metabolic reprogramming of microglia involve the uptake, breakdown, and production of fructose. Fructose enters the cell via the fructose transporter GLUT5 (encoded by *SLC2A5*), which, in the brain, is predominantly expressed by microglia [25–27]. The first step in fructolysis is the conversion of fructose to fructose-1-phosphate (F1P) by ketohexokinase (KHK), which is also abundantly expressed by microglia [26, 27]. In peripheral tissues, the breakdown of fructose is well-known to contribute to metabolic reprogramming via cellular energy depletion [28], the generation of reactive oxygen species (ROS) [29], and lipid accumulation [30, 31], recapitulating the metabolic reprogramming and microglial dysfunction observed in AD [21, 32–34]. Although fructose metabolism in microglia has been remarkably understudied, several recent findings have shown that blocking fructose metabolism may improve microglial function [35, 36]. In addition, the notion that enhanced fructose metabolism may contribute to the metabolic reprogramming of microglia is also consistent with recent studies identifying *SLC2A5* within a 'microglia-specific' module linked to late-onset-AD pathology [37] and Aβ accumulation [38]. This review will explore the role of fructose metabolism in microglia and evaluate recent work investigating whether fructose metabolism is a rational target to broadly improve microglial function for the treatment of AD.

Metabolic heterogeneity of microglia in AD

Since Rio Hortega's first identification of microglia, he and others proposed that microglia become activated in pathological conditions [39, 40]. These early observations led to an 'activated' versus 'resting' paradigm [41, 42]. However, findings from RNA sequencing (RNAseq) highlighted the metabolic, and therefore functional, complexity of microglial phenotypes, calling binary frameworks into question [43]. Single-cell RNAseq (scRNAseq) has further highlighted this complexity, revealing unique microglial subclusters associated with aging and AD i.e. disease-associated microglia (DAM) [44], and lipid-droplet associated microglia (LDAM) [13, 45]. These microglial phenotypic clusters do not fit within classical or alternative paradigms of microglial activation. Interestingly, many of these microglial clusters exhibit transcriptomic signatures indicative of elevated metabolic pathways. For example, DAMs which preferentially phagocytose Aβ, are characterized by the expression of genes associated with lipid and lipoprotein metabolism such as lipoprotein lipase (*Lpl*), *ApoE*, secreted phosphoprotein/ osteopontin (*Spp1*), and triggering receptor expressed on myeloid cells 2 (*Trem2*) [44]. Increased expression of these factors implies lipid processing is elevated in microglia to meet the increased bioenergetic needs associated with Aβ accumulation and AD pathology. In addition, Sala Frigerio et al. showed that particular microglia subgroups upregulate hypoxia-inducible factor 1α (*HIF1α*), *ApoE* and *Lpl* in response to Aβ, supporting the notion that microglia undergo metabolic reprogramming as AD progresses [46]. These studies highlight a mechanistic link between metabolic processes and phenotypic transition, which could be a strategic therapeutic target for AD.

Microglial metabolic reprogramming

Microglia shift their substrate utilization to meet the increased bioenergetic demands of executing their immune functions in the brain. To do this, they utilize glucose and glutamine to produce adenosine triphosphate (ATP), depending on substrate availability within the microenvironment [36, 47]. Although not empirically defined, microglial expression of enzymes and transporters involved in fatty acid, amino acid, and lactate metabolism suggests that microglia have the capability to switch fuel sources depending on their immunometabolic state [48]. However, because glucose is the most bioavailable substrate in the brain, microglia primarily use OXPHOS and glycolysis to generate ATP [47].

The first step in glucose utilization requires glucose transporters (GLUTs), such as GLUT1, 3, 4, 6, 8, 9, 10, 12, and 13. Despite their name, these transporters are also capable of transporting other substrates besides glucose. Of these, only GLUT4, 8, and 12 are dependent on or sensitive to insulin [49–52]. However, insulin sensitivity for each GLUT has not been determined for all cell types and requires further study. The primary glucose transporter in microglia is GLUT1, which is further elevated upon inflammatory stimulation by lipopolysaccharide (LPS) and interferon gamma (IFNγ), indicating its role in immunometabolic polarization [53]. Once inside the cell, glucose is broken down to pyruvate through glycolysis, which primarily takes place in the cytosol. This process rapidly produces energy but can only generate

a small amount of ATP per molecule of glucose and is therefore, relatively inefficient [54] (Fig. 1). Under normal oxygen conditions, pyruvate enters the mitochondria and is converted to acetyl-CoA by pyruvate dehydrogenase (PDH), which enters the tricarboxylic acid (TCA) cycle. After a series of reactions in the TCA cycle, citrate is converted to oxaloacetic acid, guanosine diphosphate (GDP) is phosphorylated to guanosine triphosphate (GTP), and NAD + and FAD gain electrons. NADH and $FADH_2$ are then available as metabolic cofactors to provide electrons to the mitochondrial enzymes in the electron transport chain (ETC). This leads to a build-up of protons in the mitochondrial membrane and the generation of ATP by ATP synthase (ETC complex V) (Fig. 1). In brief, OXPHOS describes the oxidation of NADH and $FADH_2$, in combination with ADP phosphorylation (ATP generation), that occurs in the mitochondria. While the cytosolic component of glycolysis also produces energy, OXPHOS is able to efficiently generate large amounts of ATP.

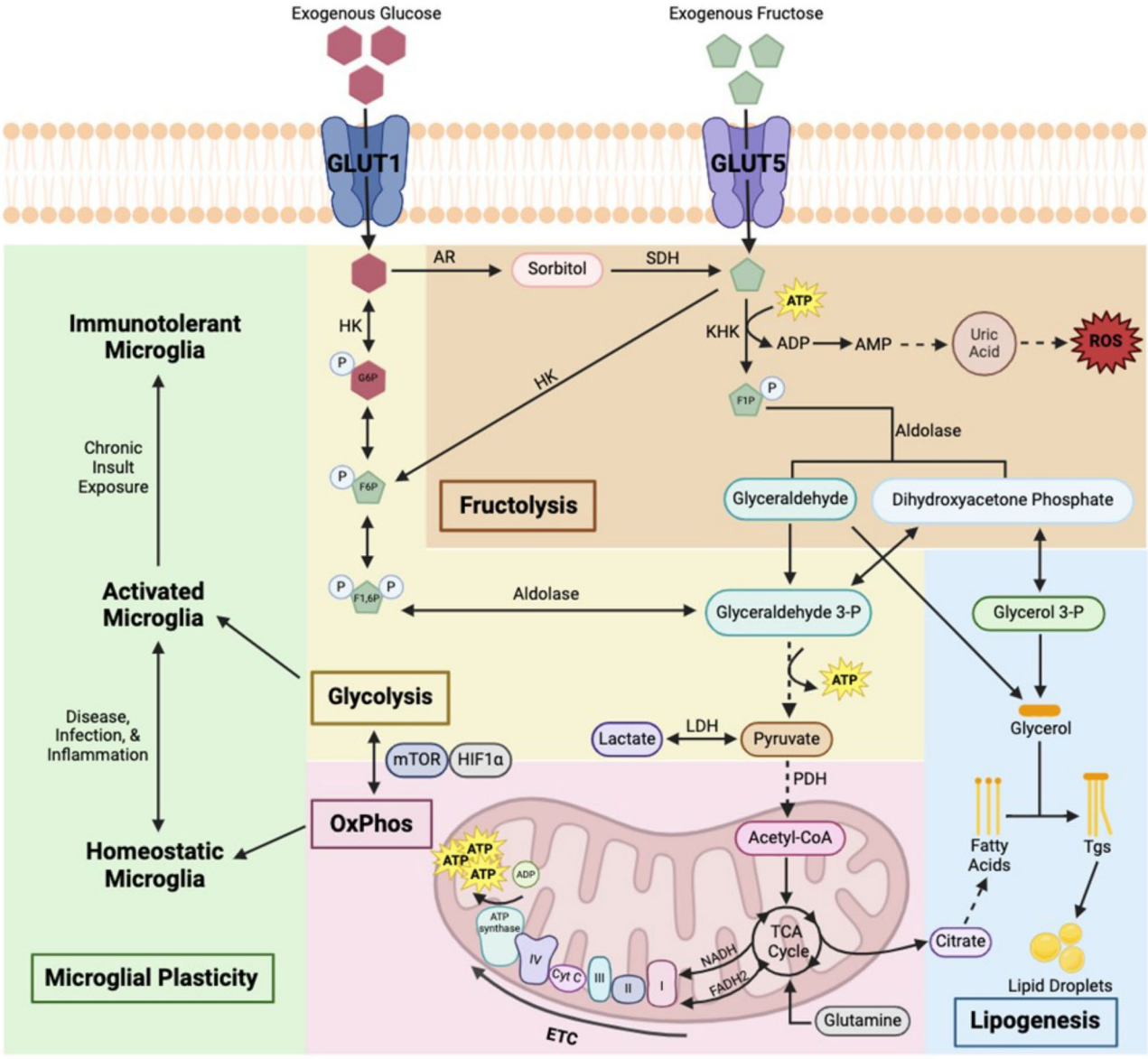

Fig. 1 Fructolysis facilitates metabolic plasticity in microglia. Glucose enters the cell via GLUT1 and is converted to pyruvate in glycolysis. This process quickly generates small amounts of ATP. Pyruvate can then enter the mitochondria to begin OXPHOS, which efficiently produces large amounts of ATP. OXPHOS is most prominent in homeostatic microglia, whereas aged and diseased microglia shift towards glycolysis. Increased fructolysis may contribute to glycolysis via the generation of glyceraldehyde 3-P. Glycolytic byproducts can also be shunted into lactate production and lipogenesis. Additionally, fructolysis generates uric acid and ROS, which drive inflammation. Shifts between OXPHOS and glycolysis involve the mTOR-HIF1α pathway. Dotted arrows represent pathways that have been simplified for clarity

Under hypoxic conditions, the lack of O_2 impairs proper OXPHOS in the mitochondria and thus, the majority of ATP production relies on glycolysis. This leads to pyruvate build-up as well as the conversion of pyruvate to lactate by lactate dehydrogenase (LDH) in the cytosol. (Fig. 1). However, lactate can also be converted back to pyruvate due to its inflammatory state and other epigenetic and energetic factors. The flux between lactate and pyruvate may be particularly beneficial in microglia, considering recent reports showing that lactic acid build-up contributes to LD accumulation [55]. Several recent studies have also shown that microglia increase the transport of lactate into the cell following LPS stimulation and injury [56, 57]. Since lactate can contribute to the pool of pyruvate that enters the TCA cycle, this suggests that lactate may help sustain energy demands in times of increased activation and signaling [58]. In addition to lactate utilization, in low glucose conditions, microglia may also utilize glutamine, a precursor to the excitatory neurotransmitter glutamate, to drive OXPHOS and ATP production [47].

The metabolic plasticity described above allows cells to meet the increased bioenergetic demands of specific stimuli. Typically, metabolic shifts are reversible, and cells return to a metabolic baseline once insults have been resolved. In microglia, this metabolic reprogramming is reminiscent of the Warburg effect, shifting from OXPHOS to glycolysis as their primary source of energy production [21, 59, 60]. Metabolic reprogramming can be triggered by disease-associated inflammation, genetic variants that modify metabolism, like ApoE4 [61], or insults like LPS [24] and Aβ [21]. For example, RNA-seq analysis of microglia acutely exposed to LPS and Aβ has shown upregulated pro-inflammatory and glycolytic genes, such as *IL-1α*, *Nfkbia*, *Ccl4*, *Ccl5*, *IL1β*, *and TNFα* [21, 24]. Similarly, MitoSox and CellROX analysis of LPS-treated cells indicated an increase in ROS, suggesting impaired mitochondrial function, reduced OXPHOS, and metabolic reprogramming [24, 59].

Although a shift from OXPHOS to glycolysis is a conceptually simple paradigm, recent findings have indicated that the metabolic states of microglia in aging and disease are not binary, supporting the notion of metabolic heterogeneity. Specifically, in vitro and in vivo work have described the presence of microglia that become exhausted after chronic exposure to noxious stimuli, are less likely to initiate an immune response, and are otherwise immunotolerant (Fig. 1). Such immunotolerant cells display defects in both glycolysis and OXPHOS. For example, in vitro studies showed that microglia chronically exposed to Aβ exhibit impaired OXPHOS and glycolysis, as well as decreased pro-inflammatory and phagocytotic responses [21]. Similarly, transcriptomic analysis of immunotolerant microglia revealed an impaired immune response in chronic (24 h) LPS treatment compared to acute (4 h) treatment, concomitant with downregulation of genes involved in OXPHOS and glycolysis [24].

Further studies have shown that dysregulated, immunotolerant microglia may also play a role in AD progression. Live, in vivo tracking has shown that when microglia from wild-type mice are exposed to acute intracranial Aβ, they rapidly respond to the site of injury [21]. However, in aged 5xFAD mice, which are chronically exposed to profound Aβ load, microglia recruitment to an injury site was significantly reduced. This decrease in microglia mobility supports the idea that chronic Aβ exposure dysregulates microglia and eventually renders them immunotolerant [21]. Notably, these immunotolerant cells were further characterized by downregulated glycolysis *and* OXPHOS [21]. Taken together, these findings suggest that microglial metabolic reprogramming in AD may be more complex than prevailing paradigms suggest, highlighting the need to identify specific master regulators of microglial metabolism that can provide both mechanistic insight and therapeutic targets going forward.

Candidate targets are the mammalian target of rapamycin (mTOR) and HIF-1α, which have been shown to regulate metabolic plasticity in microglia [21, 47, 60, 62, 63]. For example, LPS-activated microglia display increased mTOR activation and ROS production [62]. Moreover, LPS-mediated mTOR activation leads to upregulated glycolysis-related genes and downregulated OXPHOS-related genes [62]. However, when mTOR was inhibited, ROS-mediated inflammation was suppressed, suggesting the metabolic shifts that provide energy for microglia activation and inflammation are mTOR dependent [62]. Hence, more research that clarifies which metabolic pathways are responsible for mTOR activation is needed. Nonetheless, a recent study in pancreatic ductal adenocarcinoma cancer cells has shown that the AMP-activated protein kinase-mTOR pathway can be activated by increased fructose metabolism, which can in turn inhibit glucose deficiency-induced cell death. Notably, these pancreatic cancer cells highly express the fructose transporter, GLUT5, suggesting that fructose utilization promotes cell survival through metabolic plasticity. Whether a similar mechanism exists in microglia, will be an important area of study going forward [64].

Furthermore, work from our group and others have shown that microglial metabolic reprogramming is sexually dimorphic and that these differences may involve increased fructose metabolism. Transcriptomic and metabolic assays have shown that while young female microglia are less glycolytic than their male counterparts, glycolysis is markedly upregulated in female microglia with aging and AD [65, 66]. Overall, aging

and disease-associated metabolic programming do not appear to be as pronounced in male microglia [65, 66]. This is potentially due to the protective effects of estrogen, as estrogen supplementation can reduce the expression of DAM genes and increase OXPHOS [65, 67]. Additionally, *SLC2A5* is upregulated in female monocyte-derived microglia when compared to age-matched males but is reduced following estrogen supplementation [65]. This suggests that increased fructose transport may drive age-associated metabolic dysfunction in microglia, particularly in females, and may be pertinent to the pursuit of mechanisms driving increased AD risk in females [5].

Despite the potential role of fructose uptake in regulating microglial metabolism and function, how fructose is transported into and broken down by the cell is unknown. Here we provide an overview of canonical fructose processing, and how it may interact with other pathways pertinent to microglial metabolism and AD.

Fructose transport

Fructose is a simple sugar that can either be endogenously produced or transported into cells. Dietary fructose is primarily metabolized in the liver and small intestine [68] and can be transported in and out of the cells by specific GLUTs. The primary fructose-specific transporter is GLUT5, which is encoded by solute carrier family 2 member 5 (*SLC2A5*). Fructose specificity for this transporter was originally demonstrated in *Xenopus laevis* oocytes injected with synthetic human *SLC2A5* mRNA, which showed their uptake of [^{14}C]fructose can only be outcompeted by fructose and not glucose, galactose, or sucrose [69]. According to tryptophan fluorescence quenching assays, rat GLUT5 has a K_D for fructose around 6–9 mM, indicating a generally weak binding interaction [70]. Despite this, GLUT5 knockout mice develop serious nutrient-absorptive defects when fed a high-fructose diet [71]. This observation, combined with GLUT5's high specificity for fructose and abundance in the small intestine and liver, suggests that GLUT5 is primarily responsible for peripheral dietary fructose transport [71]. However, transcriptomic data from mice and humans indicate that GLUT5 may also transport fructose within the brain, particularly in microglia [26, 27]. In fact, GLUT5 expression is so specific to microglia in the brain that it has been used as a reliable microglial marker in histological and transcriptomic studies [25, 72]. When compared to GLUT1, the primary glucose transporter, the ratio of *SLC2A1*:*SLC2A5* RNA in microglia is 46.6±5.8:222.9±1.6 FPKM in mice and 0.5±0.1:52.3±7.8 FPKM in humans. This suggests that fructose may be transported into microglia more than glucose.

Despite high *SLC2A5*, tracing studies suggest that fructose transport *into* the brain is minimal compared to glucose at baseline. Fructose tracing experiments have shown that only trace amounts of peripheral fructose can enter the central nervous system (CNS) [68, 73, 74]. For example, when equal amounts of unlabeled glucose and U-^{13}C-fructose were intravenously infused in mice, 0 nmol/mg of labeled F1P was found in the brain, compared to 0.1–0.2 nmol/mg found in the liver, kidneys, and intestines [68]. These findings corroborate early circulating fructose tracing experiments in rats, which also reported low uptake of D-fructose-^{14}C in the brain, 1.75±0.32, compared to D-glucose-^{14}C, 33±3, as measured by a brain uptake index from ^{14}C to ^{3}H ratios [73]. However ^{1}H NMR analysis of human patient cerebrospinal fluid (CSF) indicates that fructose is consistently found in CSF samples at an average concentration of 160±91 μM. This is supported by additional measures of CSF fructose, which average 240±20 μM across various techniques, suggesting that fructose is present in the CNS [75]. Despite this, the amount of fructose in the CSF is still minimal compared to glucose, which averages 2960±1110 μM in ^{1}H NMR analysis and 5390±1650 μM across other metabolomic techniques [75]. While recent fructose PET and fructose labeling studies have also shown very low levels of fructose in the brain at baseline, they have also reported a significant increase in cerebral fructose after a single injection of LPS or high-fructose diet exposure [35, 76]. Therefore, it is plausible to speculate that while fructose transport into the brain is minimal, transport may be elevated in response to inflammatory stimuli and altered metabolic requirements.

Lastly, while it is largely assumed that GLUT5 expression is correlated with increased fructose transport into the cell, the structure of an inward-facing GLUT5 has also been reported [70]. Because the GLUT transporters operate in a concentration-dependent manner, we cannot say for certain the primary directionality of fructose movement through GLUT5 in microglia [70]. Given the evidence of GLUT5 expression in microglia, this suggests that GLUT5 may also be able to pump fructose out of microglia. The lack of cerebral fructose abundance and transport in non-inflammatory conditions gives rise to speculation that fructose is primarily produced endogenously in the brain, and perhaps, microglia [77].

Endogenous fructose production

Fructose is endogenously produced from glucose by the polyol pathway. The first step in the polyol pathway converts glucose to sorbitol via NADPH-dependent aldose reductase (AR). Sorbitol is then metabolized to fructose via sorbitol dehydrogenase (SDH) [31, 34] (Fig. 1).

Historically, AR has been defined as a rate-limiting enzyme whose expression is primarily located in the inner medulla and papilla of the kidney [78]. In the kidney, AR produces sorbitol that is used as a compatible organic

osmolyte to compensate for extracellular hypertonic conditions allowing for proper urinary concentration [79, 80]. However, even though AR under physiological conditions is primarily located in renal hypertonic areas, its expression can be induced outside the kidneys by multiple pathogenic factors, including hypoxia and hyperglycemia, which are common risk factors for AD [81, 82]. In this regard, AR expression in the brain has been reported and is thought to mediate Aβ-induced microglial activation [83]. However, the genetics of AR are complex, as it is part of a larger superfamily of nearly 150 enzymes [84, 85]. Additionally, it is present on chromosome 6B1 in mice and chromosome 7q35 in humans [85–87], resulting in different isoforms across species. Namely, *AKR1B1* and *AKR1B0* in humans and *Akr1b3* and *Akr1b8* in mice [26] (Table 1). Although early work suggests that AR is conserved across species and is found ubiquitously in tissue [88], the tissue-specific expression and functionality of AR isoforms have been remarkably understudied.

Regardless, like fructolysis, endogenously produced fructose is capable of inducing detrimental metabolic changes in the body [31, 89]. However, despite the established role of increased glucose uptake and glycolysis in aged and diseased microglia, the role of the polyol pathway in AD has been relatively overlooked. Nonetheless, recent work has sought to uncover the role of endogenous fructose production in the brain by measuring intracerebral fructose and glucose levels in humans using [1]H magnetic resonance spectroscopy and comparing them to their respective plasma levels [74]. Notably, intracerebral fructose levels increase after intracerebral glucose, but before plasma fructose levels, empirically showing that fructose can be endogenously generated from glucose via the polyol pathway in the human brain [74]. Further support of polyol pathway activation in the CNS comes from work demonstrating measurable sorbitol levels in CSF [90–92]. This suggests that endogenous fructose production majorly contributes to the fructose found in CSF and the brain [74].

Furthermore, support for the idea that elevated endogenous fructose can contribute to AD progression comes from a study in which several-fold increases in polyol pathway metabolites were found in post-mortem brain samples from AD patients [89]. Interestingly, one control patient had significantly increased concentrations of glucose, sorbitol, and fructose in their brain despite having no clinical manifestation of dementia [89]. This patient was ultimately diagnosed with preclinical AD postmortem [89]. This suggests that CNS polyol pathway activity precedes the cognitive impacts of AD progression and highlights the need for studies that therapeutically inhibit endogenous fructose production to slow disease progression.

Fructose metabolism

Once inside the cell, fructose is broken down in an insulin-independent manner. Fructolysis is initiated by KHK, also known as fructokinase, which converts fructose to F1P by adding a phosphate group from ATP (Fig. 1). Importantly, unlike other sugar kinases, KHK activity is not negatively regulated [93]. Fructose phosphorylation by KHK occurs rapidly, leading to transient ATP depletion and AMP generation. The accumulation of AMP activates AMP deaminase as part of the purine degradation pathway that eventually generates uric acid [94] (Fig. 1). This pathway prevents the cell from generating more ATP, which maintains a state of intracellular ATP depletion, elevated uric acid, oxidative stress, inflammation, and decreased mitochondrial function [29, 30, 36, 94, 95]. Ultimately, this pushes the cell away from

Table 1 RNA sequencing provides evidence for fructose metabolism in microglia[a]

Human				Mouse			
Gene	***Protein***	***Expressed***	***Specific***	***Gene***	***Protein***	***Expressed***	***Specific***
AKR1B1	Aldose reductase	Yes	Yes	*Akr1b3*	Aldose reductase	Yes	Yes
AKR1B10	Small intestine reductase/ AR-like protein 1	Yes	No	*Akr1b8*	Aldose reductase	Yes	No
ALDOA	Aldolase A	Yes	Yes	*Aldoa*	Aldolase A	Yes	No
ALDOB	Aldolase B	Yes	No	*Aldob*	Aldolase B	Yes	No
ALDOC	Aldolase C	Yes	No	*Aldoc*	Aldolase C	Yes	No
HK1	Hexokinase 1	Yes	No	*Hk1*	Hexokinase 1	Yes	No
HK2	Hexokinase 2	Yes	Yes	*Hk2*	Hexokinase 2	Yes	Yes
HK3	Hexokinase 3	Yes	No	*Hk3*	Hexokinase 3	Yes	Yes
GCK	Glucokinase	Yes	No	*Gck*	Glucokinase	Yes	No
*KHK**	Ketohexokinase	Yes	No	*Khk**	Ketohexokinase	Yes	Yes
SLC2A1	Glucose transporter 1	Yes	No	*Slc2a1*	Glucose transporter 1	Yes	No
SLC2A5	Glucose transporter 5	Yes	Yes	*Slc2a5*	Glucose transporter 5	Yes	Yes
SORD	Sorbitol dehydrogenase	Yes	No	*Sord*	Sorbitol dehydrogenase	Yes	Yes

*The relative expression of different KHK isoforms in microglia is unknown

[a] [24, 25].

oxidative metabolism and towards glycolysis, reminiscent of the metabolic reprogramming described above.

Interestingly, fructolysis-mediated energy depletion depends on the tissue-specific and isoform-specific expression of KHK. KHK-C is more common in the liver, intestines, and kidneys, with a high affinity for fructose [96], and therefore, an increased propensity to deplete cellular ATP. In contrast, KHK-A has a lower, ubiquitous expression pattern and a much lower affinity for fructose [96]. Interestingly, KHK-A is the primary isoform expressed in the brain [96]. While it has not been empirically determined, this implies that KHK-A is also the primary isoform present in microglia. Of note, metabolic shifts also appear to be dependent on spliceosome-directed KHK isoform expression [97, 98]. For example, in hepatocytes, KHK-C expression switches to KHK-A expression during the progression of hepatocellular carcinoma. Due to the lower affinity for fructose, this isoform switch leads to decreased amounts of fructolysis, ATP depletion, and ROS production, promoting cellular viability [99]. Given the relevance of metabolic reprogramming and plasticity in microglia and AD, further studies are needed to determine isoform-specific expression of KHK in microglia in aging and disease.

After KHK generates F1P, aldolase enzymes break F1P into either dihydroxyacetone phosphate or glyceraldehyde, which have different metabolic fates. Both dihydroxyacetone phosphate and glyceraldehyde can be converted to glyceraldehyde-3-phosphate (G3P) (Fig. 1). G3P enters the glycolysis pathway (see above section), generating pyruvate that enters the mitochondria and contributes to the pool of acetyl-CoA. While mitochondrial acetyl-CoA can be used to drive OXPHOS, cytosolic acetyl-CoA can be shunted towards fatty acid synthesis. If the conditions are favorable, fatty acids can then be esterified to generate triglycerides (Tgs). Since the fructolysis intermediates glyceraldehyde and dihydroxyacetone phosphate can also be readily converted into glycerol-3-phosphate (glycerol-3-P) and glycerol, this provides the backbone required for Tg synthesis and de novo lipogenesis (Fig. 1) [100–102]. Therefore, while glycolysis contributes to lipogenesis, fructolysis provides a source of glycerol more efficiently (Fig. 1). Since the accumulation of neutral lipids such as Tgs in lipid droplets is a hallmark of microglial dysfunction [2, 13], it is plausible to suggest that fructose-mediated lipogenesis contributes to metabolic reprogramming in microglia. Like KHK, there are several isoforms of aldolase. Aldolase A is predominantly expressed in the muscle, aldolase B in the liver and kidneys, and aldolase C is abundantly expressed in the brain [103].

Apart from KHK-mediated fructolysis, fructose may also be phosphorylated to fructose-6-P (F6P) by hexokinases (HKs). HK has four isoforms, HK1, HK2, HK3, and HK4, also known as glucokinase (GCK) [26, 104]. F6P is then converted to fructose-1,6-P (F1,6P), which can further drive glycolysis or glycogen synthesis, depending on the energetic status of the cells. HKs have a higher affinity for glucose compared to fructose [105, 106], and have a lower affinity for fructose compared to KHK [107], suggesting that HK-mediated fructose processing is minor in comparison to the canonical pathway described above. However, *HK2/Hk2* is predominately expressed by microglia in the brain and has been shown to control microglial function in diseases like AD by modulating lipid metabolism, mitochondrial activity, and Aβ clearing [26, 108–110]. While it is likely that HK2 impacts microglial function via its rate-limiting regulation of glycolysis, the flux between KHK and HK-mediated pathways remains to be empirically determined.

Lastly, fructolysis may drive immunometabolic dysfunction in microglia due to the generation of pro-inflammatory byproducts. Specifically, uric acid has been shown to increase NF-kB-mediated pro-inflammatory cytokines through ROS production and mitochondrial oxidative stress [29, 30]. Furthermore, prolonged fructose consumption in humans leads to increased systemic pro-inflammatory markers like MCP-2, PAI-1, and E-selectin. Additional short-term fructose feeding studies indicated that both young and adult rats develop hippocampal inflammation characterized by increased LPS and TNFα [111, 112]. The impact of dietary fructose on cerebral inflammation suggests that peripheral fructose may indeed reach the CNS without an existing inflammatory insult and supports the idea that fructose consumption can have detrimental metabolic consequences that could increase AD risk. Despite this, only a few experimental studies have addressed whether inhibiting fructose metabolism in the brain is a promising strategy to reverse the metabolic programming that contributes to disease. Overall, the field has been somewhat stymied by a poor understanding of how and where fructose is processed in the CNS.

Evidence of fructose metabolism across brain regions & microglia

Although fructose metabolism has been shown to lead to maladaptive metabolic reprogramming, it has been unclear whether specific brain regions or cells are vulnerable to these effects. Oppelt et al. investigated fructose metabolism across brain regions in mice using RNA in situ hybridization, which indicated that the cerebellum, hippocampus, and cerebral cortex have evidence of fructolysis-related enzymes [113]. These experiments highlighted the heterogeneity of fructose metabolism in the brain, as each region presented a unique gene expression profile. For example, the cerebellum showed abundant *Khk*, *Aldoc*, *Slc2a5*, and *Slc2a9* expression in the Purkinje

cell layer but not the molecular or granular layers. The cerebral cortex also expressed *Khk*, *Aldoc*, *Slc2a5*, and *Slc2a9* in all layers except for layer I. The hippocampus has high *Khk*, *Aldoc*, and *Slc2a9* expression, but appears to lack *Slc2a5* [113]. Additionally, KHK and aldolase enzyme activity is elevated in the mouse brain compared to the liver suggesting considerable fructose processing in the CNS [113]. However, these studies were unable to define cell-specific expression and activity. In contrast, recent studies have shown that microglia abundantly and specifically express various enzymes related to fructose metabolism [26, 114, 115] (Table 1).

KHK is present in microglia at low levels in humans, indistinguishable from other brain cell types. However, in mice, *Khk* has high microglia-specific expression [26, 27]. Again, while the specific *KHK* isoform(s) present in microglia have yet to be empirically determined, it can be assumed that they express *KHK-A* since this is the primary isoform expressed in the brain [96] (Table 1). *Aldoa*, encoding aldolase a, is abundant in mouse microglia and other brain cell types. *ALDOA* in humans is present in low amounts in microglia [26, 27]. Comparatively, *ALDOB*/*Aldob*, which encodes aldolase b, is present in extremely low levels in both human and mouse microglia similar to other brain cell types [26, 27]. Lastly, *ALDOC*/*Aldoc*, encoding aldolase c, is expressed in low levels in human and mouse microglia, respectively, but is more specific to astrocytes [26, 27] (Table 1). While this has yet to be empirically determined, *ALDOA* and *ALDOC* expression in microglia may drive cells toward a glycolytic fate as they have a higher affinity for F1,6P than F1P [116]. This may delay the breakdown of F1P and induce uric acid production. *SORD*, encoding sorbitol dehydrogenase, is present in low levels in human microglia compared to other brain cells, except fetal astrocytes. In mice, *Sord* is highly and specifically expressed in microglia [26, 27] (Table 1). As mentioned above, microglial expression of AR is more complex since there are many different isoforms between mice and humans [85, 86]. Humans predominantly express *AKR1B1*, which is present at high levels, primarily in microglia. The mouse equivalent, *Akr1b3*, shares this expression pattern [26, 27]. Humans also express *AKR1B10*, which is present in low levels across brain cells. The mouse equivalent, *Akr1b8*, shares this expression pattern [26, 27] (Table 1).

Despite these species-specific differences, it is clear that microglia are capable of fructose metabolism. Moreover, the correlation between increased fructose metabolism and metabolic dysfunction in aged and diseased microglia has prompted researchers to investigate whether inhibiting fructose uptake and breakdown is a viable target to restore microglial function in AD.

Targeting fructose uptake and breakdown to prevent microglial dysfunction

The distinct expression pattern of fructose-related proteins in microglia highlights fructose metabolism as a novel therapeutic target that can ameliorate the metabolic reprogramming of microglia in AD progression. KHK may be one such target due to its crucial role in fructose breakdown. In the periphery, inhibiting or knocking out KHK has been shown to have therapeutic potential for hereditary fructose intolerance [117]. In the brain, knocking out KHK in diabetic mice has been shown to decrease mitochondrial and oxidative stress in microglia, which restores normal cognitive functioning [36]. While these studies suggest that inhibiting KHK-mediated fructose breakdown has the potential to reverse metabolic reprogramming, KHK may not be an optimal target due to its ubiquitous and intracellular expression. In contrast, GLUT5 is specific to microglia and is a transmembrane protein. Additionally, GLUT5 is upregulated in diseases like cancer [118], diabetes [36, 119], cerebral HSV-1 infection [120], and AD [37, 38], suggesting that inhibiting GLUT5-mediated fructose processing could have broad therapeutic potential.

Despite its abundance, GLUT5 expression can vary across different models and experimental insults (Table 2). For example, in 5xFAD mice, scRNA-seq analysis of microglia has shown that *Slc2a5* is increased in some subpopulations of microglia but downregulated in others [38, 121] (Table 2). In human samples from LOAD individuals, signatures of immune cells and microglia are upregulated, including elevated *SLC2A5* [37]. However, AD models that promote tau accumulation as opposed to Aβ accumulation show a decrease in *Slc2a5* [122, 123] (Table 2). This suggests that *Slc2a5* is upregulated in microglia in response to increased Aβ load, consistent with previous literature [124]. Notably, studies that performed bulk transcriptomics (microarrays) and did not stratify for sex did not report an increase in *Slc2a5* [125] (Table 2). Since we have previously shown that *SLC2A5* is increased in monocyte-derived microglia-like cells from 55-year-old females, compared to 55-year-old males, and *Slc2a5* is increased in microglia isolated from 20-month-old female mice compared to males [65], it is reasonable to suggest that elevated GLUT5 is sex, and age dependent. This is further supported by findings from menopause-like-induced aged female mice, which exhibited an 8-fold increase in hippocampal *Slc2a5* in ApoE4 knock-in animals compared to ApoE3 [127], highlighting the interaction between ApoE and GLUT5 in the metabolic reprogramming of microglia; exacerbated in females with aging. Consistent with the notion that GLUT5 may be elevated in paradigms of metabolic programming, *Slc2a5* is upregulated in the brains of 35-day-old and 12-month-old fructose-fed rats, suggesting that paradigms of

Table 2 Fructose metabolism-related signatures in microglia across AD and AD-related models

Model	Species	Analysis Method	Differentially Regulated Pathways & Genes	References
5xFAD microglia, 8 months	Mouse	scRNA-seq, snRNA-seq	Up: *Slc2a5*	Narges et al., 2024 [38]
LOAD vs. non-demented brain, PFC	Human	Bayesian network derived co-expression modules	Up: Immune / microglia cells (*SLC2A5)*	Zhang et al., 2013 [37]
Monocyte-derived microglia-like cells, 55 year old female	Human	rtPCR	Up: *SLC2A5*	Cleland et al., 2024 [65]
Cd11b+ microglia, 20 month old females	Mouse	Bulk RNAseq	Up: *Slc2a5*, *Apoe*	Cleland et al., 2024 [65]
20% fructose-fed male brains, 35 days old	Rat	rtPCR IF staining	Up: *Slc2a5* (whole brain) Up: *Slc2a5* (hippocampus)	Shu et al., 2006 [126]
20% fructose-fed male brains, 12 months	Rat	rtPCR	Up: *Slc2a5*	Shu et al., 2006 [126]
Senescence-Accelerated Mouse Prone 8 aging model, females	Mouse	CITE-seq	Up: Metabolism (*Slc2a5*, *Apoe)*	Gruel et al., 2024 [128]
HSV-1 infected CD11b+ microglia, VPL	Mouse	scRNA-seq	Up: Carbohydrate derivative binding (*Slc2a5)*	Uyar et al., 2022 [120]
VCD-induced menopausal hippocampus with human ApoE4, 8-12 month old females	Mice	rtPCR	Up: Metabolic/Bioenergetic (*Aldob*, *Slc2a5)*	Pontifex et al., 2022 [127]
APPswe/PS1de9 cortical microglia, 15-18 month	Mouse	Expression profiling by array	Up: *Aldoa*, *Slc2a1*, *Sord*	Orre et al., 2014* [125]
			Down: *Slc2a5*, *Slc2a1*, *Aldoc*, *Hk1*, *Hk3*, *Khk*	
Tau-P301S hippocampal CD11b+ cells, 6 months	Mouse	RNA-seq	Up: *Aldoa*	Friedman et al., 2018* [123]
			Down: *Slc2a5*	
Cortical CD11b+ cells from LPS injected mice	Mouse	RNA-seq	Up: *Slc2a1*	Srinivasan et al., 2016* [122]
			Down: *Slc2a5*	

*This data was browsed using the Brain Myeloid Landscape resource provided by Srinivasan et al., 2020 [27]

high-fructose feeding and western diets may be an appropriate model to study how GLUT5-mediated fructose processing contributes to the metabolic programming of microglia, cellular dysfunction and AD neuropathogenesis [126](Table 2).

Despite the potential role of GLUT5 in modulating microglial metabolism and function in AD, studies pharmacologically targeting GLUT5 are only now emerging. Preliminary work has highlighted the ability of GLUT5 to modulate metabolism in peripheral diseases like cancer [129, 130], metabolic syndrome [131], and diabetes [119]. This is largely due to the identification of N-[4-(methylsulfonyl)-2-nitrophenyl]-1,3- benzodioxol-5-amine (MSNBA), a specific inhibitor of GLUT5. MSNBA can inhibit GLUT5 in MCF7 breast cancer cells, which are otherwise associated with elevated GLUT5 expression and fructose metabolism [129]. Additionally, MSNBA has been used to validate the inhibition of GLUT5 and fructose uptake as a potential treatment for colon cancer. Treating HT-29 colon cancer cells with MSNBA decreases their viability but does not affect the viability of noncancerous colon epithelial cells, even in the presence of fructose [130]. GLUT5 is also elevated in metabolic syndrome and diabetes. Individuals with diabetes have elevated muscle *SLC2A5* mRNA and GLUT5 protein expression compared to healthy controls. However, after 8 weeks of treatment with pioglitazone, a known insulin sensitizer, *SLC2A5* mRNA and GLUT5 protein levels decreased by 52% and 40%, respectively [119]. Since GLUT5 is insulin-independent [52], it is plausible to speculate that elevated GLUT5 is a response to increased circulating glucose in diabetes.

The specificity of GLUT5 and its ability to modulate peripheral disease and metabolism highlights its potential to be a microglia-specific target for AD. Recent work has outlined the interaction between microglial GLUT5 and neuroinflammation by showing that increased glucose concentrations lead to elevated microglial activation and pro-inflammatory gene expression [72]. Interestingly, this pathological state can be partially modulated using the fructose-mimetic GLUT5 inhibitor, 2,5-anhydro-D-mannitol [72]. In further support, in vitro and in vivo studies of GLUT5 in neonatal mice show that constitutive deletion of GLUT5 rescues the metabolic reprogramming and phagocytotic dysfunction that occurs in microglia in response to high fructose exposure [35]. Wang et al. investigated neonates from dams fed a high fructose diet and observed disrupted microglial

morphology, metabolism, and phagocytosis, along with increased *Slc2a5* mRNA and GLUT5 protein [35]. Interestingly, these effects of dietary fructose on microglia metabolism and phagocytosis were reversed in *Slc2a5*-deficient neonates, supporting the idea that targeting GLUT5 can rescue fructose-mediated metabolic reprogramming in microglia [35]. While these early studies are promising, there is still considerable work to be done to validate GLUT5 as a therapeutic target.

However, endogenous fructose production in the brain cannot be overlooked when considering novel therapeutic targets that modulate fructose processing. Therefore, it is important to consider the role of AR, the primary enzyme responsible for endogenous fructose production from glucose. Research investigating the link between AR and inflammation has made AR inhibitors an appealing therapeutic strategy to treat inflammatory pathologies like AD. For example, when mice receive systemic LPS, AR inhibitors attenuated increases in serum, retina, and whole-eye pro-inflammatory cytokines, like IL-6 and TNF-α, as well as restored microglial migration [132, 133]. These pharmacological studies were supported by experiments with constitutive AR knock-out mice, providing further evidence for AR-mediated anti-inflammatory effects [132]. Furthermore, inhibition of AR either pharmacologically or through siRNA also attenuated LPS-induced increases in pro-inflammatory cytokines in RAW264.7 murine macrophages [133–135], isolated peritoneal murine macrophages [133, 135], or retinal microglia [135]. Lastly, AR inhibition has recently been shown to attenuate the pro-inflammatory signaling induced by Aβ in microglia [83, 136]. This AR-mediated decrease in microglia inflammation provides more support for the possibility of AR in mediating inflammatory polarization and having therapeutic potential in AD.

In addition to targeting transporters and enzymes directly, there may be therapeutic benefits in reducing dietary fructose as well. Current literature links intracerebral fructose levels to AD pathology and suggests that reducing fructose consumption has the potential to treat AD at early and late stages [137–139]. Specifically, clinical studies used food-frequency questionnaires to show that patients who consumed high amounts of fructose have a higher risk of AD compared to individuals with lower fructose consumption [139]. This was recapitulated at a cellular level, as mice fed a high fructose diet showed early signs of neurodegeneration and gliosis in the hippocampus [138]. Interestingly, high fructose diets led to mitochondrial impairment and oxidative stress, which are associated with microglial activation. Encouragingly, removing fructose from the diet has been shown to reverse the deleterious effects of short-term fructose feeding by attenuating neuroinflammation [111].

Besides decreased fructose intake, other dietary supplements may also provide therapeutic benefits for AD. For example, adding cinnamon to a high fat/high fructose diet in rats attenuated the amount of AD-associated *Pten*, *Tau*, and amyloid precursor protein (*App*) mRNA [140]. Furthermore, rats supplemented with cinnamon also maintained proper insulin sensitivity, increased activity during a Y maze, and decreased anxiety during an elevated plus-maze, suggesting additional cognitive benefits [140]. Furthermore, administering decaffeinated green coffee bean extract to rats who were primed with a high fructose diet appeared to decrease oxidative damage and Aβ accumulation [141]. These neuroprotective effects were strengthened by adding pioglitazone to this regimen, which also improved learning and memory [141]. This suggests that combining dietary interventions and small-molecule drugs may provide maximum benefits.

Altogether, these studies suggest that dietary interventions or novel fructose-related drugs may be effective in attenuating AD progression. Furthermore, the therapeutic effects of any dietary changes may be enhanced by additional drugs, suggesting the need for a multi-hit treatment for AD. This approach of combination therapeutics for AD is particularly relevant for Western countries like the United States, which has rapidly increased their fructose consumption due to the prevalence of high-fructose corn syrup in foods [131, 142].

Conclusions

Overall, this review highlights the importance of fructose metabolism in driving microglial metabolic reprogramming in AD. The heterogeneous nature of microglial metabolism allows them to rapidly switch their metabolic substrate usage as well as their primary pathway for ATP production. Current literature suggests that in disease contexts, microglia shift away from OXPHOS and towards glycolysis. Emerging data suggests that this is propagated by the breakdown of fructose in microglia. The abundant expression of genes necessary for fructose uptake and breakdown supports this notion and suggests that targeting these pathways may have therapeutic benefits for AD. However, the link between fructolysis, microglial metabolism, and AD is not fully clear, and the field is missing fundamental studies that empirically define region and cell-specific fructose uptake and breakdown in the CNS. Nonetheless, these initial promising findings suggest that fructose enzymes and transporters are viable pharmacological targets to mitigate microglial metabolic reprogramming that may underly AD onset and progression. To help prioritize future work, we have outlined the top critical remaining questions in the field of microglia, fructose metabolism, and AD.

- What are the specific regulators of microglial metabolism that can provide both mechanistic insight and therapeutic targets for AD?
- How do the main pathways of fructose uptake and breakdown in the brain and microglia compare to the periphery?
- What is the relationship between dietary and endogenous fructose metabolism as they relate to AD progression?
- What is the best model to study fructose transport and breakdown in the context of AD?

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid beta
LD	lipid droplet
OXPHOS	Oxidative phosphorylation
APOE	Apolipoprotein E
F1P	Fructose-1-phosphate
KHK	Ketohexokinase
ROS	Reactive oxygen species
scRNAseq	seq-Single-cell RNA sequencing
RNAseq	RNA sequencing
DAM	Disease-associated microglia
PAM	Proliferative region-associated microglia
LDAM	Lipid droplet-associated microglia
LPL	Lipoprotein lipase
SPP1	Secreted Phosphoprotein / Osteopontin
TREM2	Triggering receptor expressed on myeloid cells 2
HIF1α	Hypoxia-inducible factor 1α
ATP	Adenosine triphosphate
GLUT	Glucose transporter
LPS	Lipopolysaccharide
IFNy	Interferon gamma
PDH	Pyruvate dehydrogenase
TCA	Tricarboxylic acid cycle
GDP	Guanosine diphosphate
GTP	Guanosine triphosphate
ETC	Electron transport chain
LDH	Lactate dehydrogenase
MTOR	Mammalian target of rapamycin
SLC2A5	Solute carrier family 2 member 5
CNS	Central nervous system
CSF	Cerebrospinal fluid
AR	Aldose reductase
SDH	Sorbitol dehydrogenase
G3P	Glyceraldehyde 3-phosphate
TGs	Triglycerides
F6P	Fructose-6-phosphate
HK	Hexokinase
GCK	Glucokinase
F1, 6P	Fructose-1,6-P
snRNA-seq	Single-nucleus RNA sequencing
rtPCR	Reverse transcription polymerase chain reaction
IF	Immunofluorescence
CITE	seq-Cellular indexing of transcriptomes and epitopes by sequencing
MSBNA	N-[4-(methylsulfonyl)-2-nitrophenyl]-1,3-benzodioxol-5-amine

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Declarations

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