Review Article / Derleme Makalesi

DOI: 10.61845/agrimedical.1527141

# A disease-based perspective of the relationship between neuroinflammation and impaired glucose metabolism

## Nöroinflamasyon ile bozulmuş glikoz metabolizması arasındaki ilişkiye hastalık temelli bakış

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**ABSTRACT**

Neuroinflammation is a significant contributor to the pathogenesis of several central nervous system disorders including Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, and amyotrophic lateral sclerosis. Neuroinflammation is the immune response of the central nervous system against central or peripheral abnormalities disturbed by foreign agents, molecules, metabolic activities, or various diseases. Astrocytes and microglia activation are the main activators of neuroinflammation. The polarization changes of these defender cells have some key roles in bodily metabolism as much as neuronal behavior. The blood-brain barrier is known as the first defender of brain parenchyma. Neuroinflammation disrupts blood-brain barrier integrity and may cause blood-brain barrier breakdown. Glucose is the main energy source of brain and glucose uptake is achieved through the blood-brain barrier. Altered glucose metabolism may have detrimental effects on brain functions and may cause brain disorders. Also, it has been suggested that neuroinflammation may have crucial roles in glucose metabolism. The distribution of the blood-brain barrier in vascular endothelial cells of neurons, astrocytes, and microglia contributes to the transport of glucose to the cells of brain. Microglia and astrocyte polarization are suggested as the two main underlying mechanisms in neuroinflammation. It's obviously determined that neuroinflammation-caused neurodegenerative diseases are tightly linked with the brain insulin resistance and disrupted cerebral and peripheral glucose metabolism. However, there is lacking knowledge about glucose metabolism deficiencies and microglia/astrocyte polarization. Herein this review, we summarized the neuroinflammation and glucose metabolism with the most common neurological diseases and the possible effects of microglia/astrocyte polarization on glucose metabolism.

Keywords: Neuroinflammation, glucose metabolism, microglia, astrocyte, neurodegeneration, neurological disorders

**ÖZ**

Nöroinflamasyon, Alzheimer Hastalığı, Parkinson Hastalığı, Huntington Hastalığı ve amiyotrofik lateral skleroz gibi birçok merkezi sinir sistemi bozukluğunun patogenezine önemli bir katkıda bulunur. Nöroinflamasyon, merkezi sinir sisteminin yabancı ajanlar, moleküller, metabolik aktiviteler veya çeşitli hastalıklar tarafından bozulmuş merkezi veya periferik anormalliklere karşı verdiği bağışıklık tepkisidir. Astroglia ve mikroglia aktivasyonu, nöroinflamasyonun ana tetikleyicileridir. Bu savunucu hücrelerin polarizasyon değişiklikleri, sinirsel davranış kadar vücut metabolizmasında da önemli roller oynar. Kan-beyin bariyeri, beyin parankimasının ilk savunucusu olarak bilinir. Nöroinflamasyon, kan-beyin bariyerinin bütünlüğünü bozar ve kan-beyin bariyerinin yıkılmasına neden olabilir. Glikoz, beynin ana enerji kaynağıdır ve glikoz alımı kan-beyin bariyeri aracılığıyla sağlanır. Bozulmuş glikoz metabolizması, beyin fonksiyonları üzerinde zararlı etkilere sahip olabilir ve beyin bozukluklarına yol açabilir. Ayrıca, nöroinflamasyonun glikoz metabolizmasında önemli bir rol oynayabileceği öne sürülmüştür. Kan-beyin bariyerinin nöronlar, astroglia ve mikroglianın vasküler endotelyal hücrelerindeki dağılımı, glikozun beyin hücrelerine taşınmasına katkıda bulunur. Mikroglia ve astroglia polarizasyonu, nöroinflamasyonun altında yatan iki ana mekanizma olarak öne sürülmüştür. Nöroinflamasyon kaynaklı nörodejeneratif hastalıkların beyin insülin direnci ve bozulmuş beyin ve periferik glikoz metabolizması ile yakından ilişkili olduğu açıkça belirlenmiştir. Bununla birlikte, glikoz metabolizması bozuklukları ve mikroglia/astroglia polarizasyonu hakkında yeterli bilgi bulunmamaktadır. Bu derlemede, en yaygın nörolojik hastalıklarla birlikte nöroinflamasyon ve glikoz metabolizması ile mikroglia/astroglia polarizasyonunun glikoz metabolizması üzerindeki olası etkilerini özetledik.

Anahtar Kelimeler: Nöroinflamasyon, glikoz metabolizması, mikroglia, astrosit, nörodejenerasyon, nörolojik bozukluklar

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Gönderilme Tarihi: 05/08/2024
Kabul Tarihi: 18/10/2024
Yayınlanma Tarihi: 30/10/2024

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Cite this article: Ovalı MA, Perçin S. A disease-based perspective of the relationship between neuroinflammation and impaired glucose metabolism. Ağrı Med J. 2024; 2(3): 132-"36.

## Introduction

Neuroinflammation is directly related to neurons, microglia, and astrocytes in the central nervous system (CNS) and has a wide range of disorders, including impaired neuroinflammatory responses that can be seen in these structures (Figure 1). Microglial activity and complex neuroinflammatory pathways may develop depending on age as well as environmental and genetic factors (1). Cytokines, chemokines, reactive oxygen species and secondary messengers are of great importance in the development process of neuroinflammation. Any event that triggered the inflammation in the brain parenchyma might be the starter of inflammation. Moreover, systemic inflammation apart from CNS may also contribute to the inflammatory process in the brain. Based on systemic inflammation in astrocytes, microglia, and blood-brain barrier (BBB) endothelial cells and inflammatory agents release are some of the causes of BBB breakdown and neuroinflammation (2). Microglia and astrocytes are major components of inflammatory processes in the CNS. Their polarizations exerts inflammatory or proinflammatory activities such as microglia polarizations to M1 (pro-inflammatory) or M2 (anti-inflammatory) and A1 (pro-inflammatory) or A2 (anti-inflammatory) cells for astrocytes. Due to the different polarizations under various conditions, the balance between pro-inflammatory and inflammatory processes varies in almost different disorders. Microglia are a type of glial cells and are mostly related to brain inflammation and inflammatory neurodegenerative diseases. Derived from macrophages, microglia are the first indications of neuroinflammation (Figure 2). Depending on the polarization as mentioned above, pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, proteases, and other cytokines also have adverse effects on the integrity of the BBB have deleterious effects in neurodegenerative diseases. Inactivated microglia become activated in response to released cytokines. One of the most important activities of microglia is transferring nutrients to the CNS (3).

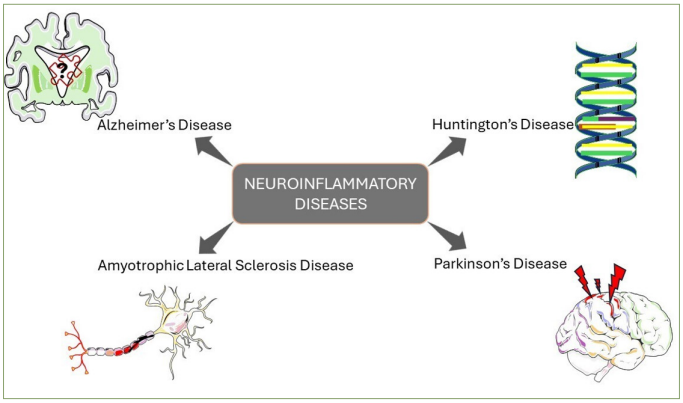


Figure 1. Common neuroinflammatory diseases. Aβ accumulations lead to neuroinflammation in Alzheimer's Disease. In Huntington's Disease neuroinflammation triggers infiltration of peripheral immüne cells to the CNS. Chronic neuroinflammation is one of the hallmarks of Parkinson's Disease localized in dopamşnergic neurons. ALS is motor neuron disease. Neuroinflammation causes progressive degeneration of nerve cells in the CNS (The figures were prepared using the website https://smart.servier.com and Microsoft PowerPoint).

Neuroinflammation is a complexity of activity and triggers the release of many agents for the initiation of the inflammatory processes. Many responsible molecules of this pathway are released under inflammatory conditions (4). As it is well known NF-κB is the controller of inflammation, apoptosis, and cell survival and modulates expressions of the genes in the response of immune and inflammatory processes. Further, NF-κB promotes neuronal survival and plasticity, too. One of the activators of NF-κB during the inflammatory process is the toll-like receptor (TLR) which initiates the inflammatory process, activating signaling molecules such as NF-κB to activate the release of cytokines. In addition, recent studies claimed that cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) pathways are tightly associated with neuroinflammation and neurodegeneration. Cytokine release directly interacts with these mentioned pathways whereas COX-1 has a strong involvement in neuroinflammation compared to COX-2 (1).

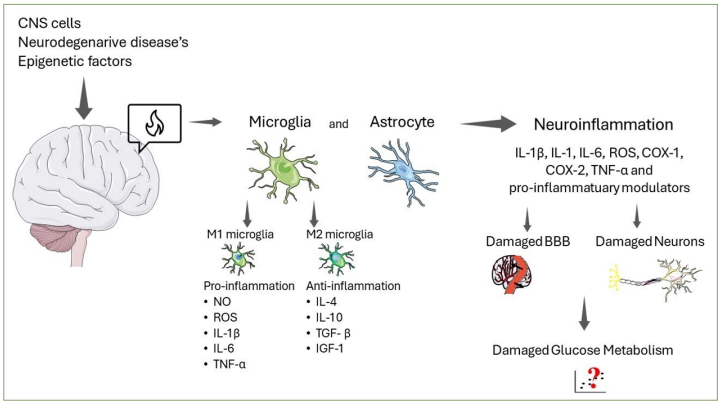


Figure 2. During neurodegenerative damage caused by infectious conditions and/or as a result of epigenetic factors of neurons in the central nervous system, the resting microglia gets activated. Activated microglia play a key role in pro-inflammatory (M1) and anti-inflammatory (M2) states. The cytokines present in these stages of neuroinflammatory responses. Resting astrocytes are activated through cellular crosstalk with microglia. Activation of microglia and astrocytes stimulates the neuroinflammatory response. Neuroinflammation can lead to neuronal damage, blood-brain barrier disruption, and impaired glucose metabolism (BBB: blood-brain barrier) (The figures were prepared using the website https://smart.servier.com and Microsoft PowerPoint).

Glucose is the most abundant energy source for CNS and the survival of microglia survival. Additionally, many glucose transporters are expressed on the microglia membrane to provide adequate glucose uptake (5). Similarly to microglia, astrocytes have several key roles in CNS functions. In addition to the development of the brain, astrocytes maintain the BBB structure. Astrocytes are one of the essential players of brain development provide synapse growth, modulate neuronal activity, synapse and neurotransmission regulation and are responsible for the maintenance of BBB structure. Astrocytes are key factors for metabolic events in the brain (3). Furthermore, astrocytes are the first structures for their metabolic support of neurons. The neurons could not store the glycogen, astrocytes provide the main energy stock for neurons by themselves. When the CNS gets damaged, astrocyte proliferation is activated and undergoes morphological changes. Astrocytes are not only triggering the inflammatory responses and worsening the tissue damage but also facilitating immunosuppression processes (6). Astrocytes are involved in transporting glucose and glucose metabolites from capillaries to the hypothalamus to distal neurons in the CNS (7). During neuroinflammation, the polarization of astrocytes may affect glucose metabolism and brain nutrition through astrocyte activities. Astrocytes behave as glucose sensors during food intake and regulate the energy balance. In a study, intra-arterial injection of glucose to the carotid artery indicated that, glucose transporter 2 (GLUT2) is the initial way of glucose and highly expressed in astrocytes. In addition, it is well known that the insulin receptor (IR) is indispensable for glucose uptake, and expressed astrocytes which is mainly required for the entry of glucose into the brain. In an in vitro study, downregulation of IR in astrocytes decrease the expression of GLUTs (8). Hence, the astrocyte end-feet covers the whole surface of the tissue capillary and tightly in collaboration with capillaries, GLUT1 expressed in this site facilitates the glucose uptake. So, it is clear from the

mentioned outcomes that the overall brain glucose metabolism is based on neuronal and astrocyte activities (9).

## Brain-Glucose metabolism

Glucose is one of the indispensable energy sources for cerebral functions. Glucose uptake provides adenosine triphosphate (ATP) production, avoids oxidative stress, regulates neuronal function and survival, and maintains brain structure neurotransmitter synthesis. The brain continuously needs glucose, and glucose must be supplied uninterruptedly. The brain gains ATP from glucose for energy supply and prevention of oxidative stress. The requirement for more glucose enhances cerebral blood flow and cerebral metabolic rates. While the brain's main energy source is glucose, lactate also can be counted as the source of energy supply. During glycolysis, glucose is transferred into lactate, and neurons use lactate for energy supply. Enhanced glycolysis in astrocytes contributes to lactate release to extracellular space for ATP production (10). Glucose is the most predominant fuel of brain functions through the production of ATP for neuronal maintenance and neurotransmitters. The growing brain consumes the more abundant amount of glucose from the body, and an adult brain uptake 20-25% of the total amount of glucose. The brain is the more expensive organ in terms of glucose usage for various neuronal activities including neuronal action potentials, and synaptic transmissions. Glucose uptake in the brain is modulated by specific family members of GLUTs. There are various GLUT members placed such as GLUT1 on BBB, GLUT3, 4, 6, 8 expressed on neurons, GLUT 1, 3, 4, 5, 6, 8, 9, 10, 12, and 13 on microglia (11). One of the main causes of neuroinflammatory and neurodegenerative disorders is altered glucose uptake and metabolism. The abnormality in the expression of vascular GLUT1, neuronal GLUT3, and GLUT4 is also associated with disrupted brain glucose metabolism (10). It is clear from the number of GLUTs expressed in CNS that glucose is essential for brain functions (Figure 3).

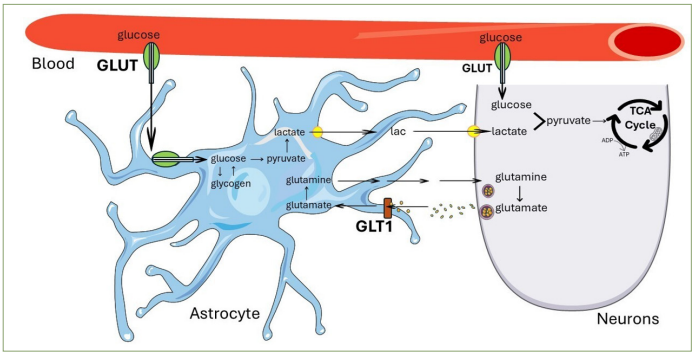


Figure 3. Astrocytes take glucose form blood capillaries via GLUTs. Following glucose uptake, astrocytes store as glucose oras in glycogen form or metabolized into pyruvate, which is then utilized in the tricarboxylic acid cycle (TCA) for aerobic energy production within mitochondria. Simultaneously glucose is also received by neurons directly from capillaries for energy source through glycolysis (The figures were prepared using the website https://smart.servier.com and Microsoft PowerPoint).

Alteration of glucose metabolism has many deleterious effects on brain functions and is related to pathologies in the brain including hypoglycemia, hyperglycemia, neurodegeneration, apoptosis, and cognitive dysfunction. Thus, it was previously proved that balanced serum glucose levels are indispensable for neuronal activity. Due to the heterogeneous cells of the brain and cell-specific glucose metabolism claims that metabolic events in the brain are drived in a complex manner. Specific pathways including Wnt, GSK-3β, PI3K-AKT, and AMPK; and hexokinase 2, acetyl-CoA, and enolase 2 enzymes seem to be responsible for this metabolic modulation. Blood glucose is mainly regulated by the hypothalamus and the pituitary maintaining blood glucose balance, in collaboration with the cortex and striatum. The brain tissue has glucose-sensitive neurons itself. These neurons are in crosstalk with other glucose metabolism-related organs such as the kidney, liver, intestines, and pancreas. In addition, insulin receptors are widely distributed in the different regions of the brain. That means the brain has an important role in systemic glucose metabolism. Also, it was clarified that systemic glucose metabolism disorders decline brain glucose consumption through inhibition of GLUT activity. Glucose metabolism alteration is one of the early reasons for neurological disorders especially in stroke, Alzheimer's disease (AD), and Parkinson's disease (PD). In an experimental stroke model in mice, infarcted areas had increased glucose levels (11, 12). Additionally, it was observed that altered cerebral insulin activities worsen neuronal degeneration. It can be suggested that cell type specificities against glucose metabolism contribute to the pathogenesis of neuroinflammatory diseases (11).

## Astrocytes and glucose metabolism

Astrocytes are promoters of brain functions, and the number of astrocytes is higher than neurons. Astrocytes support neurons via regulation of glutamate homeostasis, storing glycogen, water imbalance, neurotransmission, synaptic activity and remodeling and tissue repair (13). During glucose uptake, astrocytes became more active to produce glycolytic enzymes for energy supply and provides glucose by glycolysis. Astrocytes act as a driving force for the use of lactate from the extracellular space. Moreover, astrocytes stimulate lactate transfer to pyruvate after being included in the tricarboxylic acid cycle (TCA) cycle (9).

## Neuroinflammatory diseases associated with glucose metabolism disorders

Brain and glucose metabolism-related brain or systemic glucose metabolism disorders may trigger together to the development of neurological dysfunction including neuroinflammation. The most widely seen neuroinflammatory diseases among the public are AD, PD, Huntington's Disease (HD), and amyotrophic lateral sclerosis (ALS) (14). Now, all the above-mentioned diseases will be discussed around glucose metabolism disorders extent.

## Alzheimer's Disease

AD is one of the worldwide common neurological disorders and is generally elucidated by the amyloid-β (Aβ) accumulation in the brain tissue hypothesis. The base of this hypothesis is increased extracellular deposition of misfolded Aβ. The neuroinflammation in response to AD is primarily triggered by microglia residing in the CNS. Aβ accumulation initiates cytokine release, microglial activation, inflammatory reaction, and reactive astrocytosis. Moreover, Aβ peptides cause a range of biochemical dysfunctions characterized by synapse/neuron loss, and cerebral atrophy (15-17). It is known that cognitive disorders in AD are directly related to glycolysis metabolism as well as the brain's inability to utilize glucose properly (18,19). It is common for AD patients to have structural defects in glucose transporter proteins and insulin resistance. For example, GLUT1 and GLUT3 protein levels are significantly reduced in the brain tissues of AD patients (20,21).

As the cerebral glucose metabolism changes is one of the pathological pathways of AD pathology the clinical symptoms of AD occur in earlier periods of pathology. In AD, altered glucose metabolism emerges from different pathways. The initial signal may be the impairment of glucose transport and uptake. Additionally, the expression changes of glucose transporters may

predict to neurological disorders as in AD. The gene expression levels of glucose transporters were found to be decreased in humans and rodents. It was indicated that upregulation of Aβ due to GLUT1 downregulation could lead to BBB disruption and induce degenerative changes in neurons (22).

## Parkinson's Disease

PD is one of the most common neurodegenerative diseases in elderly people characterized by loss of muscle control. In the pathology of PD, loss of dopaminergic neurons in the substantia nigra pars compacta comes to the fore. It is reported that the imbalance in dopamine metabolism caused by oxidative stress significantly contributes to the development of this disease (23).

Previous studies claimed that there is a broad crosstalk between energy metabolism and PD. Altered glucose metabolism in PD patients was reported as high as 50%-80% (T2DM) (24). Particularly, hyperglycemia is the most seen manifestation in most PD patients. In the early stages of PD, patients exhibit different symptoms of glucose metabolism disorders such as weight loss or gain and decreased or no food intake. Glucose metabolism abnormality has been identified in PD. Brain neurons exhibit impaired glucose metabolism, even at early stages of PD (25).

Impaired glucose metabolism was also defined in PD pathophysiology as one of the non-motor symptoms. In humans, different brain regions showed altered glucose metabolism widely distributed in cerebral regions. In a study established on PD patients, while decreased glucose metabolic activity was observed that presented in temporal, and frontal focal areas, increased glucose metabolism was presented in the sensorimotor cortex, cerebellum, and deep regions of the brain. However, there is still not a consensus on glucose metabolism-related brain activity changes of PD pathophysiology. Further experimental studies are required to clarify this argumentative issue (10).

## Huntington's Disease

The inherited and progressive loss of brain functions disorder called as HD which is a devastating disease in which patients suffer from uncontrolled movements, and intellectual disabilities (23). Abnormalities in glucose homeostasis, acting as a metabolic stress factor due to energy deficiency, have been demonstrated in numerous studies on HD. It is also known that HD patients have a higher prevalence of impaired glucose tolerance and diabetes (26,27). On the other hand, in 2008, Lalić and colleagues conducted the first detailed investigation into glycemic control in normoglycemic HD patients. This study primarily demonstrated reduced insulin sensitivity, increased insulin resistance, impaired insulin secretion, and the relationship of insulin response (28). HD was attributed directly to energy metabolism, body weight, glucose homeostasis, and organ-specific subcellular abnormalities (29). HD patients displayed desensitized insulin activity and abnormal insulin secretion. There is substantial evidence that the peripheral symptoms of HD are tightly linked to endocrine and metabolic impairments. Several studies suggest a high prevalence of glucose intolerance and diabetes mellitus in patients with HD (30). In HD pathogenesis, disrupted brain metabolic activity is still a challenge that must be mainly clarified (29). Studies about HD pathophysiology in humans and animals indicated that metabolic symptoms of HD such as weight loss and malnutrition may be linked to altered peripheral metabolic activity. Limited studies reported increased diabetes population among HD patients and suggested that it could be easily detected by biochemical analysis through measurement of blood micronutrients measurement (30). Mitochondrial oxidative stress was suggested as a crucial mechanism for glucose metabolism impairment in the brain tissue of HD patients (19). As a result, critical determinants in the progression of the disease include energy deficit, oxidative stress, unexplained weight loss, increased insulin resistance, and a lack of essential metabolic substrates (31).

## Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disease characterized by progressive degeneration of neurons and has high mortality rates (32). Most ALS patients experience metabolic disorders such as weight loss and malnutrition. The energy balance of ALS patients generally seemed to be altered mostly linked to hypermetabolism and disturbed nutrition (33). Further, neurons are highly vulnerable to energy imbalance and require high energy sources for axonal and neuronal networks. Disruption of the energy uptake mechanism may directly negatively affect the survival and activities of neurons (34). Hypermetabolism is considered one of the hallmarks of ALS which leads to glycogen accumulation (33). Glycogen is mainly stored in astrocytes and abnormal degradation of glycogen triggers the accumulation of glycogen. In addition, human familial ALS patients have gained reduced and limited energy from glycogen. It was previously suggested that glucose metabolism disorders may be an abnormality in ALS due to muscle wasting or physical inactivity (32). In vivo ALS models have shown that glucose uptake is significantly reduced in the spinal cord, including the motor, frontal, and occipital cortex (35). Inhibiting glycogen synthesis or promoting its breakdown in the spinal cord may offer therapeutic benefits for ALS patients. However, further research is needed to understand how astrocytic glycogen accumulation impacts energy availability and cytokine release. Glycogen-targeted therapeutic strategies have already demonstrated preclinical success in Lafora disease (LD) mouse models and could potentially be tested in ALS models (36). Multiple observations indicate that this heightened glycogen accumulation might play a role in the pathophysiology of ALS. Duran et al demonstrated that excessive glycogen buildup is pathological in both astrocytes and neurons (37). Astrocytic glycogen accumulation drives neuroinflammation in LD but not in epilepsy. Given that glycogen buildup in neurons and astrocytes contributes to the pathophysiology of LD, it is possible that similar glycogen accumulation could have pathological effects in other neurological disorders, such as ALS (38).

## Conclusion and future perspective

In this review, a disease-based approach to neuroinflammation and impaired glucose metabolism is presented. In this context, information is provided about the impaired glucose metabolism processes in many diseases closely associated with neuroinflammation. The information provided about the prevalence of high-glucose diets in our age and the potential development of neuroinflammatory diseases as a result is of great importance. Studies show that neuroinflammation is one of the main causes of the progression of various neurological disorders such as AD, PD and ALS. The fact that glucose is the main energy source of the brain reveals the importance of impaired glucose metabolism in the central nervous system in the treatment or diagnosis of these diseases. Therefore, it would not be a coincidence that brain functions are related to CNS and peripheral glucose metabolism. As mentioned in this review, BBB integrity is disrupted during neuroinflammation, and microglia and astrocyte activation triggers the inflammatory process. The devastating effects of neuroinflammation not only cause damage to brain functions, but also disrupt glucose uptake through the BBB, leading to further deterioration of the condition. Disturbances in glucose metabolism are clearly evident

in neuroinflammatory diseases, but detailed molecular studies are needed to define the underlying pathological mechanisms between neurodegeneration and glucose metabolism disorders. Therefore, revealing the pathological mechanisms of these diseases in detail will also guide researchers for treatment methods. It is clear that molecular-level and mechanism-focused studies are needed to elucidate the relationship between neuroinflammation and impaired glucose metabolism and to contribute to treatment processes. Through this review, we provide researchers interested in this field with fundamental information that serves as a concise overview.

## Conflict of Interest

There is no conflict of interest

## Funding

There is no funding support for this study

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