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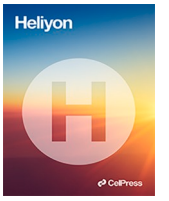

Review article

Astrocyte mitochondria: Potential therapeutic targets for epilepsy

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ABSTRACT

Epilepsy is a chronic, relapsing neurological disorder, and current treatments focus primarily on neurons, yet one-third of patients still develop drug-resistant epilepsy. Therefore, there is an urgent need to explore new therapeutic targets. Interestingly, astrocytes can transfer their healthy mitochondria into neighboring neurons, thus preventing neuronal damage. Astrocyte mitochondria have been shown to have a therapeutic role in stroke and neurodegenerative diseases. However, their therapeutic effect in epilepsy and its related mechanisms have been less studied. In this review, we mainly summarize the regulatory role of astrocyte mitochondria in glutamate, calcium ion, and adenosine triphosphate (ATP) homeostasis and outline the protective role of astrocyte mitochondria in nervous system diseases, revealing a new target for epilepsy treatment.

1. Introduction

Epilepsy is a chronic brain disease characterized by recurrent seizures [1] that affects approximately 1 % of the world's population, with a threefold increase in premature mortality compared to the general population. Most previous research has focused on how to inhibit neuronal firing and how to explain the changes in the internal electrical activity of neurons or neuronal networks that cause seizures [2]. Therefore, drug therapy has been limited to the treatment of neuronal targets. There are more than 30 antiseizure drugs (ASDs); however, one-third of epileptic patients do not respond to multiple ASDs and develop drug-resistant epilepsy [3]. Individuals suffering from drug-resistant epilepsy experience a diminished quality of life and have few treatment alternatives aside from surgery. This condition also brings about physical, psychological, and social repercussions, placing a significant burden on both families and society [4]. The loss of neurons and the formation of glial scars are two major pathological characteristics of drug-resistant epilepsy, with reactive astrocytes being the main component of glial scars [5].

In recent years, with the study of the mechanism of epileptogenesis and epilepsy development, astrocytes have been thought to play a key role [6,7]. In astrocytes from temporal lobe epilepsy (TLE) patients and animal models, the expression of neurotransmitter receptors, voltage-gated ion channels, inflammatory cytokines, and other proteins changes dramatically [8]. Reinstating the presence of the glutamate transporter1(GLT1) on astrocytes, decreasing the expression of adenosine kinase (ADK), modulating calcium and potassium ions, and restraining the hyperplasia of reactive astrocytes can effectively suppress epileptic seizures [9,10]. Accordingly, astrocyte-based epilepsy therapies may be a promising new direction.

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2. Astrocytes

Astrocytes account for 20%–40 % of the total number of brain cells and are divided into protoplasmic cells and fibrocytes according to their morphology [11]. Functionally, astrocytes have traditionally been thought to provide only structural support and neurotrophic function for the brain. In fact, astrocytes, which surround the basal membrane, pericytes, and endothelial cells, are a major component of the blood-brain barrier (BBB) and are involved in regulating the BBB and blood flow [12]. Moreover, astrocytes produce abundant mitochondrial reactive oxygen species, which can transport glycolytic metabolites such as L-serine and L-lactic acid to neurons, thereby conserving energy demand, maintaining the redox state, and thus regulating neurotransmitter activity [13]. Furthermore, astrocytes participate in the formation of tripartite synapses [14], participate in neuronal signal transduction, and regulate Ca^{2+} and K^{+} levels, subsequently releasing glial transmitters such as γ-aminobutyric acid (GABA), glutamic acid, and adenosine triphosphate (ATP), affecting neuronal excitability and regulating synaptic transmission and plasticity [15]. Therefore, astrocytes are part of tripartite synapses, which are involved in the regulation of neuronal activity.

Under pathological conditions, such as epilepsy, stroke, neurodegenerative disease, or traumatic brain injury (TBI), astrocytes rapidly respond to become reactive astrocytes, which are characterized by increased numbers and changes in expression profile, morphology, and biochemical function [16]. Depending on the model or disease, reactive astrocytes can be classified as A1 (cytotoxic), which secrete a variety of inflammatory factors that damage neurons and lead to their loss, and A2 (neuroprotective), which produce neurotrophic factors that promote neuron survival. Importantly, *in vivo*, these reactive states may coexist with spatial and temporal heterogeneity. Specifically, through single-cell sequencing, it was found that astrocytes in different disease models exhibit different cell subtypes. Spatial transcriptome found that there were also differences in astrocyte subtypes in cortical, hippocampal, white matter and other regions [17,18]. In a 4-aminopyridine-induced status epilepticus (SE) mouse model, the expression of A1 astrocyte markers C3 and a circular RNA of circIgf1r were upregulated after SE, while the A2 astrocyte marker S100A10 was not significantly changed. After injecting *circIgf1r* siRNA into the lateral ventricle, Shao et al. found that circIgf1r promotes the polarization of astrocytes towards the A1 phenotype by inhibiting autophagy [19]. Therefore, regulating the transformation of A1-and A2-type astrocytes may become a new target for epilepsy treatment. Additionally, in TLE patients and Kainic acid (KA)-induced epilepsy mouse models, Chen et al. found a new reactive astrocyte state characterized by excessive accumulation of lipid droplets in astrocytes, accompanied by elevated APOE expression, which intensified neuronal excitability [17]. Additionally, lipid accumulation accelerates mitochondrial damage [20]. In the lithium chlorine-pilocarpine-induced status epilepticus (SE) rat model, Plata et al. used sulforhodamine 101, a specific marker for astrocytes, and observed a significant increase in astrocyte density after SE. Morphologically, compared with the control group, the astrocytes were not significantly different in the size of the cell body domain, the number of primary branches or the peak number of branches in the SE group. However, the distal branch, which is thought to have many Ca^{2+} stores of organelles such as mitochondria and endoplasmic reticulum (ER), was sharply reduced [21]. Taken together, seizures contribute to morphological changes, reduce the number of ER and mitochondria in the terminal foot, impair function, and lead to Ca^{2+} imbalance in astrocytes.

3. Astrocyte mitochondria

Mitochondria are dynamic organelles responsible for regulating cell survival and apoptosis, cell energy metabolism, redox signalling, and maintaining calcium homeostasis. Their dysfunction is associated with a variety of neurological diseases, including stroke, TBI, Alzheimer's disease (AD), Parkinson's disease (PD) and epilepsy [22]. Numerous studies have found that generalized seizures are related to the mutation of mitochondrial $tRNA^{phe}$ [23], mitochondrial polymerase γ, and mitochondrial $tRNA^{Lys}$, and recent studies have shown that sporadic epilepsy is also associated with mitochondrial dysfunction [24].

As nonexcitable cells, astrocytes are thought to be energy-saving. However, an increasing number of studies have shown that astrocytes contain abundant mitochondria [25,26]. Through three-dimensional reconstruction, Aten et al. found that in addition to the absence of mitochondria in the lobules, mitochondria establish a dense tubular network from somatic to branchlets, including the end-foot process enclosing blood vessels, and pointed out that the lack of mitochondria in the lobules may be due to spatial limitations in these fine terminal processes. Interestingly, the number of mitochondria in astrocytes is comparable to that in electrically excitable neurons [27]. Additionally, in astrocyte processes, delayed fragmentation and autophagic degradation of individual mitochondria contribute to increased Ca^{2+} signaling, while mitochondrial loss in the astrocyte process is associated with a substantial increase in Ca^{2+} after oxygen-glucose deprivation [28]. Accordingly, astrocyte mitochondria are involved in regulating important biological processes.

4. Astrocyte mitochondria are involved in the regulation of neuronal excitability

Biological processes such as the glutamate-glutamine cycle, calcium ions, and ATP contribute to the excitability of neurons. Meanwhile, neuronal excitability is closely related to epileptogenesis. Therefore, astrocyte mitochondria may be involved in the pathogenesis of epilepsy because they regulate these processes as explained in the following paragraphs.

4.1. Glutamate metabolism

Glutamate, as an excitatory neurotransmitter, plays an important role in the development of epileptogenesis and is an important molecule mediating the interactions between neurons and astrocytes. When glutamate is released by the presynaptic membrane, it drives excitatory amino acid transporter-2 (EAAT-2, known as GLT-1) on astrocytes to be converted into glutamine under the action of

glutamine synthetase (GS). Glutamine is then transported extracellularly by SNAT3 transporters, followed by SNAT1 transporters to presynaptic neurons, and finally glutamine is converted to glutamate by glutaminase (GLS) [15]. EAAT2 is responsible for the recovery of approximately 90 % of glutamate in the synaptic cleft to prevent excessive accumulation of glutamate and excitatory toxicity [29]. In particular, glutamate is transported from the cytoplasm of astrocytes to mitochondria via glutamate carriers (GSs) and aspartate glutamate carriers (AGSs), which are subsequently converted to α-ketoglutarate (α-KG) by aspartate transferase via glutamate dehydrogenase (GDH), aspartate aminotransferase (AAT), alanine aminotransferase (ALAT), branched aminotransferase (BCAT) and enter the tricarboxylic acid (TCA) cycle. Additionally, in mitochondria, glutamine can be catalysed by phospho-activated glutaminase (PAG) on the outer surface of the mitochondrial inner membrane to synthesize glutamate and release ammonia [30] (Fig. 1a). In conclusion, astrocyte mitochondria contribute to the synthesis and metabolism of glutamate.

Seizures cause much glutamate to accumulate in the synaptic cleft, and astrocytes preferentially clear glutamate [31]. AFG3L2, mutated in infantile syndromes characterized by epilepsy, spastic-ataxia, and premature death, encodes a subunit of the *m*-AAA protease that regulates mitochondrial homeostasis. In mice with conditional knockout of *Afg3l2* in astrocytes, *m*-AAA deletion of Bergman glia was found, mitochondria showed mitochondrial network fragmentation and mitochondrial ridge deletion, and the glutamate transporter EAAT2 showed abnormal patchy expression, GFAP upregulation, and even excitatory toxicity [32] (Fig.2a). Likewise, GC1, the mitochondrial glutamate carrier *SLC25A22* was mutated in early epileptic encephalopathy, silenced it in primary astrocytes, and under the stimulation of glutamate, NADPH formation and ATP levels in astrocytes were reduced, accompanied by substantial glutamic acid accumulation [33]. Accordingly, mitochondria play an important role in maintaining glutamate homeostasis in astrocytes. Additionally, among eight adult mitochondrial patients, Chan et al. found that five patients had a history of epilepsy. Pathologically, astrocyte reactive hyperplasia was observed in mitochondrial patients and epileptic patients, and mitochondria in astrocytes showed downregulation of complex I and IV subunits. Subsequently, a novel model of mitochondrial epilepsy was

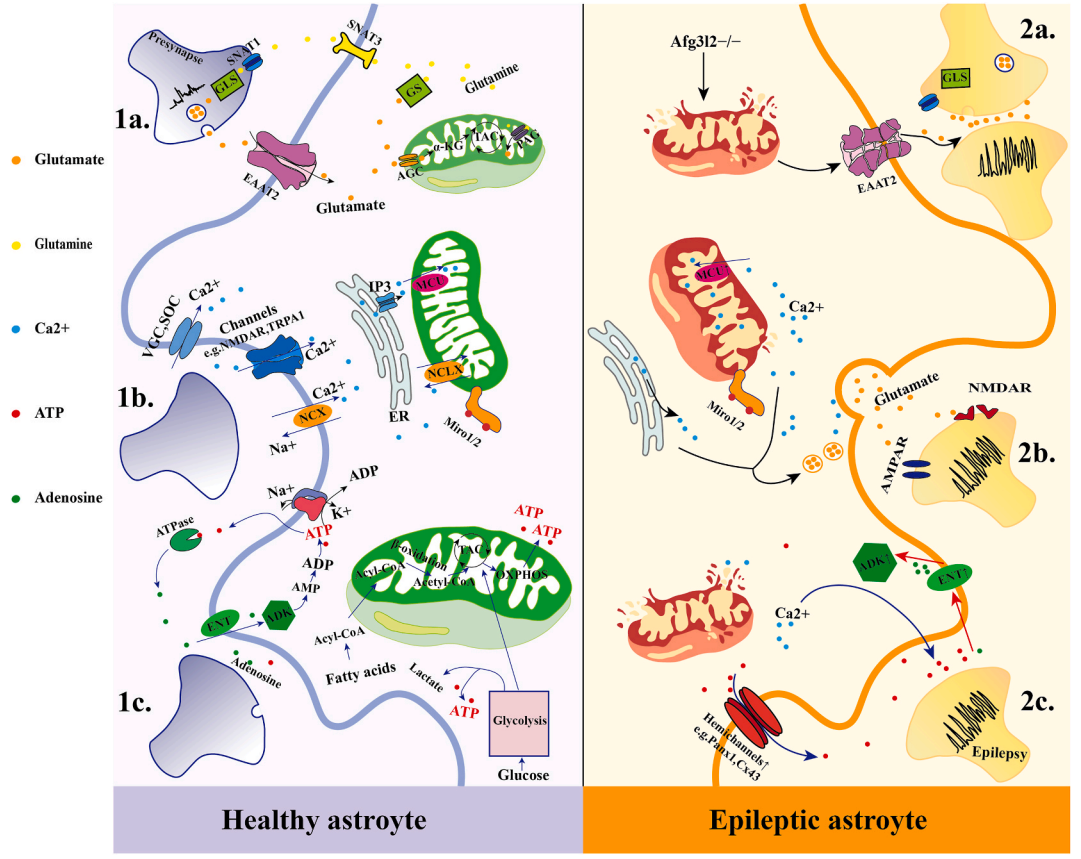

Fig. 1. The function of astrocyte mitochondria. Mitochondrial dysfunction may lead to increased susceptibility to epilepsy. (1a) The mitochondria of astrocytes regulate the glutamate-glutamine cycle. (2a) Loss of *Afg3l2* results in disruption of the mitochondrial network, loss of the mitochondrial ridge, accumulation of glutamate in the synaptic cleft, and ultimately increased neuronal excitability. (1b) Astrocyte mitochondria are involved in regulating calcium homeostasis. (2b) In animal models of epilepsy, Ca^{2+} levels within astrocytes were significantly increased. Additionally, the increased Ca^{2+} can induce the release of glutamate and increase the excitability of neurons. Inhibition of MCU on mitochondria or upregulation of Miro has antiepileptic effects. (1c) Astrocyte mitochondria take fatty acids and glucose as raw materials, producing ATP by β-oxidation and glycolysis. (2c) After epileptic insult, extracellular ATP content is significantly increased, which is mainly released by astrocytes, and hemichannels such as cox43 and panx1 that release ATP on the surface of astrocytes are also significantly increased. However, it is not clear whether astrocyte mitochondria are related to the changes in ATP content after epilepsy.

constructed *in vitro* using fluorocitrate, an enzyme of the tricarboxylic acid cycle responsible for converting citrate to isocitrate, in conjunction with mitochondrial respiratory chain complex I and IV inhibitors, rotenone, and potassium cyanide, applied to hippocampal sections. It was found that the GABA-glutamate-glutamine cycle of astrocytes plays a crucial role in the regulation of GABA-mediated inhibition [34]. Therefore, astrocyte mitochondria may be involved in the pathogenesis of epilepsy by regulating glutamate balance.

4.2. Calcium homeostasis

Calcium ions affect the excitability of neurons mainly by promoting the release of synaptic vesicles containing neurotransmitters and excitatory neurotransmitters. Astrocytes regulate ion exchange and neurotransmitter transfer between neurons and glial cells through calcium signals. Spontaneous Ca^{2+} signalling in astrocytes is thought to be caused by extracellular Ca^{2+} uptake. In contrast, stimulus-induced Ca^{2+} signalling is thought to be caused by Ca^{2+} being released into the endoplasmic reticulum via the activation of the Gq protein-coupled receptor [35]. Ca^{2+} enters astrocytes mainly in the following ways: ① Voltage-gated Ca^{2+} (VGC) channels and store-operated Ca^{2+} (SOC) channels are responsible for direct Ca^{2+} entry into astrocyte branchlets. ② Through the Na^{+}- Ca^{2+} exchanger (NCX); ③ Ion channels such as NMDAR and transient receptor potential vanilloid 1 (TRPV1) (Fig. 1b) [36]. Ca^{2+} uptake further activates the Na^{+} -K^{+}-ATPase transporter and reverses the Na^{+}- Ca^{2+} exchanger, resulting in the outflow of Na^{+} and the inflow of Ca^{2+}, which consumes ATP and leads to an increase in local Ca^{2+} concentration. The increased binding of Ca^{2+} to Ca^{2+}-dependent mitochondrial Rho (Miro) 1/2 proteins on the surface of mitochondria impedes the interaction between mitochondria and motor apparatus components, such as myosin and adaptors, thereby ultimately impacting mitochondrial movement [28]. Additionally, under physiological conditions, mitochondrial Ca^{2+} uniporters (MCUs) are mainly responsible for mediating Ca^{2+} uptake, while Na^{+}-Ca^{2+}-Li^{+} exchangers (NCLXs) are mainly responsible for mediating Ca^{2+} exportation within mitochondria. Moreover, mitochondrial Ca^{2+} signalling is tightly coupled to IP_3R-mediated Ca^{2+} release from the astrocyte endoplasmic reticulum (ER) [37].

Using patch pliers and calcium ion imaging, Go'mez-Gonzalo et al. found that Ca^{2+} elevation in astrocytes was associated with the initial development and maintenance of focal epileptiform discharges. Selective inhibition of the Ca^{2+} signal in astrocytes can block paroxysmal discharge but does not affect the generation of paroxysmal discharge [38]. In the KA-induced epilepsy model, Heuser et al. found that Ca^{2+} signal elevation in astrocytes precedes that in neurons via 2-photon imaging technology, especially in the CA1 region, which precedes neuronal 8s. In mice with type 2 inositol-1,4,5-adenosine triphosphate receptor (*Itpr2*$^{-/-}$) knockout, Ca^{2+} elevation in astrocytes was eliminated, and epileptiform activity in the knockout mice was reduced by 60 %, as measured by EEG [39]. Similarly, in a zebrafish model of drug-induced seizures, Verdugo et al. found numerous Ca^{2+} signals within astrocytes preferred to attack and indicated that activation of glial networks led to a strong increase in neural activity through the action of glutamic acid and gap junctions [40]. Additionally, sodium voltage-gated channel alpha subunit 1 (*Scn1a*), coding for $Nav_{1.1}$, a subunit of the voltage-gated sodium channel, which heterozygous mutations were exhibited in 70–80 % of Dravet syndrome (DS) patients. In a DS mouse model (a loss-of-function mutation in *Scn1a*), the transient spontaneous inflow of Ca^{2+} in astrocytes was not changed, but the slope of the Ca^{2+} peak was increased. Likewise, in response to ATP stimulation, the total amount of Ca^{2+} signaling was not changed, but the slope of instantaneous Ca^{2+} inflow and Ca^{2+} peak in Scn1a$^{+/-}$ astrocytes was increased. These results showed enhanced Ca^{2+} signaling in astrocytes in animal models of DS [41]. In summary, Ca^{2+} elevation in astrocytes has a spasmodic effect, and Ca^{2+} signaling in astrocytes is expected to be a new target for epilepsy therapy.

In astrocytes, mitochondria play a regulatory role in the concentration of Ca^{2+} in the cytoplasm [42]. In the pilocarpine-induced SE mouse model, the Racine score of mice decreased after the injection of adenovirus into the lateral ventricle upregulated miro-1, suggesting that miro-1 can affect the susceptibility of mice to epilepsy. Meanwhile, Nissl staining, TUNEL assay and the detection of apoptosis-related proteins such as cleaved caspase-3, Bax and Bcl-2 showed that miro-1 could rescue neuronal necrosis and apoptosis caused by epileptic injury, and the elevation of S100β was rescued [43]. In magnesia-free SD rat hippocampal neurons, the mitochondrial Ca^{2+} concentration increased, and the MCU inhibitor Ru360 significantly decreased the rate of apoptosis induced by epilepsy and the production of mitochondrial reactive oxygen species (ROS) and alleviated seizure-induced ER stress [44]. These processes are exacerbated by the MCU agonist spermine. In brief, upregulation of Miro or inhibition of MCU had a protective effect on the occurrence of epilepsy (Fig. 2b). However, the role of mitochondrial proteins related to Ca^{2+} regulation in epilepsy in astrocytes has not been reported.

4.3. ATP production/metabolism

Astrocytes produce adenosine triphosphate (ATP) through glycolysis and mitochondrial respiration and are responsible for 20 % of the brain's total oxygen consumption (Fig. 1c). In the mitochondria of astrocytes, the metabolic reaction of β-fatty acid oxidation (FAO) using fatty acids as raw materials may produce 3 times more energy than glycolysis [45]. Thus, astrocytes are energy-efficient cells, while more research is needed to verify whether astrocytes are more energy-efficient than other cell types. In addition to regulating the production of ATP, FAO can also participate in the synthesis of glutamate, which is then converted into glutamine and transmitted to neurons. The third role of FAO is to detoxify the fatty acids transmitted by neurons to astrocytes [46]. The primary cultured rat astrocytes contained 27.9 ± 4.7 nmol/mg ATP, which was maintained at a high level for at least 6 h in medium without glucose and amino acids and decreased by 70 % after 24 h. At 30 min after the application of the respiratory chain inhibitor antiamycin A or the mitochondrial uncoupling agent BAM-15, the high initial specific ATP content in glucose-hungry astrocytes was almost eliminated. Inhibition of mitochondrial pyruvate carrier with UK5099 alone or mitochondrial fatty acid uptake with etomoxil alone had little effect on glucose deprivation of high ATP content in astrocytes during 8-h incubation. The combined application of these two

inhibitors almost completely depleted the cell's ATP levels within 5 h [47]. This suggests that mitochondrial oxidation of pyruvate and fatty acids strongly contributes to maintaining high ATP concentrations in glucose-deprived astrocytes. In conclusion, astrocyte mitochondria play an important role in ATP production.

In addition to providing energy to cells, ATP acts as an excitatory neurotransmitter by activating a variety of purinergic P2 receptors [48]. ATP is stored in synapses and astrocyte vesicles, but it can be released from the nerve endings of neurons, dendrites, axons, or microglia and astrocytes, and is released mainly from astrocytes under excitotoxic conditions [49]. The increase in extracellular ATP in animal models of epilepsy induced by pilocarpine, kainic acid (KA) and pentylenetetrazole and in cell models induced by magnesium-free medium has been well outlined by Beamer et al. [50]. After epileptic injury, ATP is released into the cell mainly through the following mechanisms: ① destruction of cell membrane integrity; ② release through connexin 43 (Cx43) in astrocytes and pannexin-1 (Panx1) hemichannels in neurons and astrocytes; and ③ release through vesicles [51] (Fig. 2c). Through the ethidium bromide uptake test, Dossi et al. found that epileptic activity led to the activation of panx1 channels in the cortical sections of patients with epilepsy. A luciferin-luciferase luminescence assay showed that extracellular ATP content increased significantly in epileptic states and that Panx1 regulated epileptoid activities by regulating ATP release and activating the P2 receptor. Similarly, when Panx1-deficient transgenic mice were injected with KA, spontaneous epileptic seizures were reduced [52]. Furthermore, immunofluorescence double labelling of GFAP and Cx43 in the hippocampus of TLE patients revealed massive astrogliosis, accompanied by a significant increase in Cx43 [53]. TAT-Gap19 is a simulated peptide that specifically inhibits Cx43 semi-ion channels. After intraperitoneal injection, TAT-GAP19 can reverse the increase in serine levels induced by pilocarpine and play an anti-epileptic role [54]. Therefore, astrocytes influence epileptogenesis by directly regulating the production and relfigease of ATP. However, there is still a gap in the relationship between astrocyte mitochondria-ATP and epilepsy.

5. The therapeutic effect of astrocyte mitochondria

Mitochondria are organelles that can move from cell to cell. Under pathological conditions, damaged mitochondria in neurons can be transferred to astrocytes for processing. In cerebral ischemia, the oxygen supply to the mitochondria is impaired, leading to the production of excessive ROS in neurons, which eventually leads to uncontrolled cell death [55]. Meanwhile, mitochondrial dysfunction is the main cause of stroke and TBI, and the replenishment of mitochondria in neurons can rescue oxidative stress damage to a certain extent, reduce cell apoptosis, and thus improve cell survival [56] (Table 1). In animal and cellular models of TBI, Zhao et al. found that mitochondrial transplantation from liver and muscle tissue can significantly reduce neuronal apoptosis and restore the

Table 1
The therapeutic effects and related mechanisms of mitochondria in different CNS diseases.

Author (year)	Disease	Model	Mitochondria source	Findings	Relevant mechanisms
Zhao et al. (2021)	TBI	CCI model	Liver and muscle tissue mitochondria	Mitochondrial transplantation can improve the spatial memory of TBI mice, reduce anxiety, and have therapeutic effects.	Rescued neuronal apoptosis, and restored the expression of Tom20 and the phosphorylation of JNK.
Hayakawa et al. (2016)	Stroke	Mouse focal cerebral ischemia model; OGD and reoxygenation *in vitro*	Astrocytic mitochondria	Transient focal cerebral ischemia in mice led to the migration of astrocytic mitochondria into neighboring neurons, thereby enhancing cell survival signals.	A calcium-dependent mechanism that involves CD38 and cyclic ADP ribose signaling.
Ni et al. (2022)	Stroke	Mouse focal cerebral ischemia model; OGD and reoxygenation *in vitro*	Astrocytic mitochondria	Rb1 promotes neuronal function and survival by enhancing mitochondrial transfer from astrocytes.	Rb1 inhibits NADH dehydrogenase in mitochondrial complex I and blocks ROS produced by reverse electron transport in complex I.
Sun et al. (2019)	Glioma	U87 cells	Astrocytic mitochondria	Mitochondrial transfer boosted the expression of genes and proteins associated with the TCA cycle, promoted aerobic respiration, reduced glycolysis, reactivated the mitochondrial apoptotic pathway, and suppressed the malignant proliferation of U87 cells.	NAD + -CD38-cADPR-Ca2+ signaling.
Cheng et al. (2021)	PD	A rotenone induced *in vitro* PD model	iPSCs-derived astrocyte mitochondria	iPSCs-derived astrocyte mitochondria can be used as donors to reduce synaptic degeneration and axon pruning of injured DA neurons.	A phospho-p38 depended pathway.
Jia et al. (2023)	Epilepsy	Pilocarpine-induced status epilepticus in mice	The mouse hippocampus mitochondria	After the introduction of external mitochondria, the production of ROS, the proliferation of microglia and astrocytes, and the loss of hippocampal neurons were alleviated.	–

TBI, traumatic brain injury; CCI, controlled cortical impact; OGD, oxygen–glucose deprivation; ROS, reactive oxygen species; TCA, tricarboxylic acid; PD, Parkinson's Disease; iPSCs: induced pluripotent stem cell; DA, dopaminergic.

expression of Tom20 and P-JNK [57], thus having a therapeutic effect on TBI. Additionally, Hayakawa et al. found extracellular particles containing mitochondria in the conditioned medium of rat cortical astrocytes. When rat cortical neurons were deprived of oxygen–glucose, the level of intracellular ATP and the activity of neurons decreased. ATP levels increased and neuron activity was restored after astrocyte-derived conditioned medium containing extracellular mitochondrial particles was added to neurons. However, extracellular mitochondria in astrocyte-conditioned media were removed, the neuroprotective effect disappeared. Fluorescence microscopy confirmed the presence of astrocyte-derived mitochondria in neurons. Subsequently, the collected extracellular mitochondrial particles were injected into the infarct pericortex of mice with focal cerebral ischemia, and immunostaining revealed the presence of transplanted astrocyte mitochondria in neurons 24 h later [58]. Therefore, astrocytes may release extracellular mitochondrial particles into neurons, rescuing the loss of neuronal vitality after stroke. Furthermore, when neurons were damaged by oxygen–glucose deprivation and reperfusion (OGD/R), coculture with conditioned astrocyte culture medium increased neuronal membrane potential and mitochondrial oxygen consumption [59], suggesting that enhancing mitochondrial transfer in astrocytes could promote neuronal function and survival against ischaemic stroke. In addition, whether astrocyte mitochondrial transfer affects neuronal metabolism remains to be further studied.

Moreover, astrocyte mitochondria also have therapeutic effects in glioma, Parkinson's disease (PD) and other neurological diseases. Mitochondria were isolated from healthy human astrocytes and cocultured with human glioma cells (U87). Confocal microscopy and transmission electron microscopy showed that mitochondria entered U87 cells through endocytosis mediated by NAD + -CD38-cADPR-Ca^{2+} signaling and slowed the glycolysis rate of U87 cells, inhibiting the malignant proliferation of U87 cells. *In vivo*, isolated mitochondria injected into U87-inoculated tumors were found to inhibit tumor growth and increase radiosensitivity [60]. Accordingly, mitochondria derived from astrocytes have therapeutic effects on glioma. However, the mechanism of mitochondrial transplantation on the different functions of neurons and glioma cells still requires further investigation. Using imaging mass cytometry (IMC), Chen et al. demonstrated reduced signalling of many mitochondrial proteins in astrocytes of patients with PD [61]. In rotenone-induced PD cell models, induced pluripotent stem cell (iPSC)-derived astrocytes can rescue the neurodegeneration of dopaminergic neurons by releasing mitochondria and being internalized by damaged neurons via the phosphorylated p38 pathway [62]. *In vitro*, the survival rate and mitochondrial membrane potential of the primary cultured cortical neurons were reduced after coculture with cisplatin, a commonly used chemotherapy drug, and then the surviving neurons were recovered after coculture with astrocytes. It was further confirmed that the repair effect was achieved by transferring astrocyte mitochondria to damaged neurons [63]. Cisplatin therapy causes cognitive dysfunction, so we speculate that astrocyte mitochondrial transfer may also ameliorate cognitive impairment caused by epilepsy, neurodegenerative diseases such as AD, PD, and drug use. Collectively, exogenous supplementation of mitochondria released by healthy astrocytes can reverse neuronal damage and may be a new therapeutic intervention for stroke, glioma, PD and other diseases.

Impaired mitochondrial function was observed in different animal models of epilepsy. Transport driver 1 (TRAK1), a key regulator of mitochondrial motility, was reduced in TLE patient specimens and in pilocarpine-induced epileptic rat models. Knockdown of TRAK1 resulted in increased mitochondrial fission factor (MFF) *in vitro*, shortened seizure latency and increased seizure frequency. Exogenous overexpression of TRAK1 can save the dysfunction caused by TRAK1 knockdown [64]. In a Kv1.1 knockout (KO) mouse model of epilepsy, Simeone et al. found decreased respiration driven by mitochondrial respiratory complex I and increased H_2O_2 levels. Combination therapy consisting of ascorbic acid, alpha-tocopherol, and sodium pyruvate can improve mitochondrial function, reduce the frequency of seizures, and avoid severe tonic–clonic seizures induced by KA [65]. Moreover, mitochondrial dihydroorotate dehydrogenase (DHODH) is a primary target for saving metabolic homeostasis in the hyperexcitation hippocampal circuit, and its inhibitor terifluride reduces CA3-CA1 synaptic transmission, decreases the mean firing rate of neurons in the CA1 region, and reduces susceptibility to seizures [66]. Therefore, mitochondrial dysfunction plays an important role in the occurrence and development of epilepsy.

Remarkably, in almost 20 % of patients with primary mitochondrial diseases, epilepsy is the first symptom, which can manifest as any type of seizure. SE in primary mitochondrial disease often coexists with stroke-like seizures, resulting in poor prognosis and high mortality due to its treatment resistance [67]. Moreover, after feeding valproic acid (VPA) to rats for 75 days, Ponchaut et al. discovered that the decrease in mitochondrial respiration induced by VPA was attributed to the depletion of mitochondrial cytochrome *aa*3, resulting in a nearly 30 % reduction [68]. Therefore, VPA is the most well-known of mitochondrial toxic AEDs and should be used with caution in patients with POLG1 mutations or myoclonic epilepsy with ragged-red fibre (MERRF). Additionally, phenobarbital (PB), carbamazepine (CBZ), oxcarbazepine (OXC), gabapentin (GBP), etc. may affect mitochondrial metabolism, such as diminishing ATP production, reducing mitochondrial isozyme, inhibiting mitochondrial transaminase isozyme, and ultimately inducing or aggravating primary mitochondrial diseases [69]. Hence, new treatments are urgently needed for seizures associated with primary mitochondrial diseases.

Interestingly, both *in vitro* and *in vivo*, a small number of studies have found that mitochondrial transfer has a therapeutic effect on epilepsy. In a hybrid cell model constructed by fusion of human osteosarcoma 143B cells containing the A8344G mutation in mtDNA with enucleated skin fibroblast fusion from patients with clinically proven MERRF syndrome, Chang et al. found that after mitochondria were transferred by the cell-penetrating peptide Pep-1, the internalized mitochondria were maintained for 15 days in the cytology department, accompanied by cell survival and functional recovery [70]. In pilocarpine-induced SE mice, exogenous mitochondria derived from the mouse hippocampus were injected into the caudal vein for treatment. Ethologically, artificial mitochondrial transplantation can improve the cognitive dysfunction, anxiety and depression caused by SE. In terms of pathological changes, artificial mitochondrial transplantation can mitigate neuronal loss, inhibit the activation of microglia and astrocytes induced by SE [71]. However, whether the exogenous mitochondria incorporate into neurons, astrocytes or microglia, and through what mechanism affect neuronal survival and glial cell activation still need to be further explored. Notably, mitochondrial transplantation may be a new

strategy for the treatment of epilepsy and its related psychiatric cognitive dysfunction. However, there are still many research gaps regarding the extraction, dosage, injection mode of astrocyte mitochondria, and therapeutic role in different types of epilepsy.

6. Summary

Astrocytes take part in tripartite synapses and play an important role in epileptogenesis. They protect neurons from overexcitation under physiological conditions. Healthy mitochondria can transfer to damaged neurons and play a protective role. The dysfunction of astrocyte mitochondria leads to an imbalance in glutamate homeostasis, calcium homeostasis and ATP production, ultimately affecting the excitability of neurons. To date, there have been few studies on the exogenous supply of astrocytes to treat epilepsy. The role of astrocyte mitochondria in different types of epilepsy, such as TLE, mitochondrial epilepsy and drug-resistant epilepsy, and the related mechanisms need to be further studied. Importantly, epilepsy is often associated with cognitive impairment, and astrocyte mitochondrial transfer seems to be a new treatment strategy for cognitive impairment after epilepsy. Finally, disease-specific techniques for astrocyte mitochondrial health need to be explored and optimized.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Lu Chen: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Wenqian Yang:** Conceptualization. **Fei Yang:** Conceptualization. **Tingwan Xu:** Conceptualization. **Yanying Yu:** Conceptualization. **Qian Wu:** Writing – review & editing, Supervision, Conceptualization. **Yanbing Han:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A.A. Asadi-Pooya, F. Brigo, S. Lattanzi, I. Blumcke, Adult epilepsy, Lancet (2023), https://doi.org/10.1016/S0140-6736(23)01048-6. PMID: 37459868.
[2] E. Ren, G. Curia, Synaptic reshaping and neuronal outcomes in the temporal lobe epilepsy, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms22083860. PMID: 33917911.
[3] W. Loscher, H. Potschka, S.M. Sisodiya, A. Vezzani, Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options, Pharmacol. Rev. 72 (2020) 606–638, https://doi.org/10.1124/pr.120.019539. PMID: 32540959.
[4] M.T. Janson, J.L. Bainbridge, Continuing burden of refractory epilepsy, Ann. Pharmacother. 55 (2021) 406–408, https://doi.org/10.1177/1060028020948056. PMID: 32795085.
[5] M.G. Hadera, H. Eloqayli, S. Jaradat, A. Nehlig, U. Sonnewald, Astrocyte-neuronal interactions in epileptogenesis, J. Neurosci. Res. 93 (2015) 1157–1164, https://doi.org/10.1002/jnr.23584. PMID: 25782696.
[6] B.S. Purnell, M. Alves, D. Boison, Astrocyte-neuron circuits in epilepsy, Neurobiol. Dis. 179 (2023) 106058, https://doi.org/10.1016/j.nbd.2023.106058. PMID: 36868484.
[7] Q.P. Verhoog, L. Holtman, E. Aronica, E.A. van Vliet, Astrocytes as guardians of neuronal excitability: mechanisms underlying epileptogenesis, Front. Neurol. 11 (2020) 591690, https://doi.org/10.3389/fneur.2020.591690. PMID: 33324329.
[8] K.S. Wilcox, J.M. Gee, M.B. Gibbons, P. Tvrdik, J.A. White, Altered Structure and Function of Astrocytes Following Status Epilepticus, Epilepsy & Behavior, vol. 49, PMCID, 2015, pp. 17–19, https://doi.org/10.1016/j.yebeh.2015.05.002. PMC5382801.
[9] X-x Liu, L. Yang, L-x Shao, Y. He, G. Wu, Y-h Bao, N-n Lu, D-m Gong, Y-p Lu, T-t Cui, N-h Sun, D-y Chen, W-x Shi, K. Fukunaga, H-s Chen, Z. Chen, F. Han, Y-m Lu, Endothelial Cdk5 deficit leads to the development of spontaneous epilepsy through CXCL1/CXCR2-mediated reactive astrogliosis, J. Exp. Med. 217 (2020), https://doi.org/10.1084/jem.20180992. PMID: 31699822.
[10] T. Li, J.-Q. Lan, D. Boison, Uncoupling of astrogliosis from epileptogenesis in adenosine kinase (ADK) transgenic mice, Neuron Glia Biol. 4 (2009) 91–99, https://doi.org/10.1017/s1740925x09990135. PMID: 19674507.
[11] A. Wl, The neuroglia elements in the human brain, Br. Med. J. 2 (1893) 227–230, https://doi.org/10.1136/bmj.2.1700.227. PMID: 20754383.
[12] D.M. Mastorakos P, The anatomy and immunology of vasculature in the central nervous system, Sci Immunol 4 (2019) eaav0492, https://doi.org/10.1126/sciimmunol.aav0492. PMID: 31300479.
[13] G. Bonvento, J.P. Bolanos, Astrocyte-neuron metabolic cooperation shapes brain activity, Cell Metabol. 33 (2021) 1546–1564, https://doi.org/10.1016/j.cmet.2021.07.006. PMID: 34348099.
[14] G. Perea, M. Navarrete, A. Araque, Tripartite synapses: astrocytes process and control synaptic information, Trends Neurosci. 32 (2009) 421–431, https://doi.org/10.1016/j.tins.2009.05.001. PMID: 19615761.
[15] S. Satarker, S.L. Bojja, P.C. Gurram, J. Mudgal, D. Arora, M. Nampoothiri, Astrocytic glutamatergic transmission and its implications in neurodegenerative disorders, Cells 11 (2022), https://doi.org/10.3390/cells11071139. PMID: 35406702.
[16] C. Escartin, O. Guillemaud, M.A. Carrillo-de Sauvage, Questions and (some) answers on reactive astrocytes, Glia 67 (2019) 2221–2247, https://doi.org/10.1002/glia.23687. PMID: 31429127.

[17] Z.P. Chen, S. Wang, X. Zhao, W. Fang, Z. Wang, H. Ye, M.J. Wang, L. Ke, T. Huang, P. Lv, X. Jiang, Q. Zhang, L. Li, S.T. Xie, J.N. Zhu, C. Hang, D. Chen, X. Liu, C. Yan, Lipid-accumulated reactive astrocytes promote disease progression in epilepsy, Nat. Neurosci. 26 (2023) 542–554, https://doi.org/10.1038/s41593-023-01288-6. PMID: 36941428.
[18] Z. Qian, J. Qin, Y. Lai, C. Zhang, X. Zhang, Large-scale integration of single-cell RNA-seq data reveals astrocyte diversity and transcriptomic modules across six central nervous system disorders, Biomolecules 13 (2023), https://doi.org/10.3390/biom13040692. PMID: 37189441.
[19] L. Shao, G.T. Jiang, X.L. Yang, M.L. Zeng, J.J. Cheng, S. Kong, X. Dong, T.X. Chen, S. Han, J. Yin, W.H. Liu, X.H. He, C. He, B.W. Peng, Silencing of circIgf1r plays a protective role in neuronal injury via regulating astrocyte polarization during epilepsy, Faseb. J. 35 (2021) e21330, https://doi.org/10.1096/fj.202001737RR. PMID: 33417289.
[20] L. Zhang, X. Wang, W. Yu, J. Ying, P. Fang, Q. Zheng, X. Feng, J. Hu, F. Xiao, S. Chen, G. Wei, Y. Lin, X. Liu, D. Yang, Y. Fang, G. Xu, F. Hua, CB2R activation regulates TFEB-mediated autophagy and affects lipid metabolism and inflammation of astrocytes in POCD, Front. Immunol. 13 (2022) 836494, https://doi.org/10.3389/fimmu.2022.836494. PMID: 35392078.
[21] A. Plata, A. Lebedeva, P. Denisov, O. Nosova, T.Y. Postnikova, A. Pimashkin, A. Brazhe, A.V. Zaitsev, D.A. Rusakov, A. Semyanov, Astrocytic atrophy following status epilepticus parallels reduced Ca(2+) activity and impaired synaptic plasticity in the rat Hippocampus, Front. Mol. Neurosci. 11 (2018) 215, https://doi.org/10.3389/fnmol.2018.00215. PMID: 29997475.
[22] M. Falabella, H.J. Vernon, M.G. Hanna, S.M. Claypool, Pitceathly RDSCardiolipin, mitochondria, and neurological disease, Trends Endocrinol. Metabol. 32 (2021) 224–237, https://doi.org/10.1016/j.tem.2021.01.006. PMID: 33640250.
[23] G. Zsurka, K.G. Hampel, I. Nelson, C. Jardel, S.R. Mirandola, R. Sassen, C. Kornblum, P. Marcorelles, S. Lavoué, A. Lombès, K. Ws, Severe epilepsy as the major symptom of new mutations in the mitochondrial tRNAPhe gene, Neurology 74 (2010) 507–512, https://doi.org/10.1212/WNL.0b013e3181cef7ab. PMID: 20142618.
[24] J. Folbergrova, W.S. Kunz, Mitochondrial dysfunction in epilepsy, Mitochondrion 12 (2012) 35–40, https://doi.org/10.1016/j.mito.2011.04.004. PMID: 21530687.
[25] A. Agarwal, P.H. Wu, E.G. Hughes, M. Fukaya, M.A. Tischfield, A.J. Langseth, D. Wirtz, D.E. Bergles, Transient opening of the mitochondrial permeability transition pore induces microdomain calcium transients in astrocyte processes, Neuron 93 (2017) 587–605 e7, https://doi.org/10.1016/j.neuron.2016.12.034. PMID: 28132831.
[26] H. Chai, B. Diaz-Castro, E. Shigetomi, E. Monte, J.C. Octeau, X. Yu, W. Cohn, P.S. Rajendran, T.M. Vondriska, J.P. Whitelegge, G. Coppola, B.S. Khakh, Neural circuit-specialized astrocytes: transcriptomic, proteomic, morphological, and functional evidence, Neuron 95 (2017) 531–549 e9, https://doi.org/10.1016/j.neuron.2017.06.029. PMID: 28712653.
[27] S. Aten, C.M. Kiyoshi, E.P. Arzola, J.A. Patterson, A.T. Taylor, Y. Du, A.M. Guiher, M. Philip, E.G. Camacho, D. Mediratta, K. Collins, K. Boni, S.A. Garcia, R. Kumar, A.N. Drake, A. Hegazi, L. Trank, E. Benson, G. Kidd, D. Terman, M. Zhou, Ultrastructural view of astrocyte arborization, astrocyte-astrocyte and astrocyte-synapse contacts, intracellular vesicle-like structures, and mitochondrial network, Prog. Neurobiol. 213 (2022) 102264, https://doi.org/10.1016/j.pneurobio.2022.102264. PMID: 35283239.
[28] J.G. Jackson, M.B. Robinson, Regulation of mitochondrial dynamics in astrocytes: mechanisms, consequences, and unknowns, Glia 66 (2018) 1213–1234, https://doi.org/10.1002/glia.23252. PMID: 29098734.
[29] J. Goncalves-Ribeiro, C.C. Pina, A.M. Sebastiao, S.H. Vaz, Glutamate transporters in hippocampal LTD/LTP: not just prevention of excitotoxicity, Front. Cell. Neurosci. 13 (2019) 357, https://doi.org/10.3389/fncel.2019.00357. PMID: 31447647.
[30] J. Song, X. Yang, M. Zhang, C. Wang, L. Chen, Glutamate metabolism in mitochondria is closely related to Alzheimer's disease, J Alzheimers Dis 84 (2021) 557–578, https://doi.org/10.3233/JAD-210595. PMID: 34602474.
[31] G. Fiermonte, L. Palmieri, S. Todisco, G. Agrimi, F. Palmieri, J.E. Walker, Identification of the mitochondrial glutamate transporter. Bacterial expression, reconstitution, functional characterization, and tissue distribution of two human isoforms, J. Biol. Chem. 277 (2002) 19289–19294, https://doi.org/10.1074/jbc.M201572200. PMID: 11897791.
[32] S. Murru, S. Hess, E. Barth, E.R. Almajan, D. Schatton, S. Hermans, S. Brodesser, T. Langer, P. Kloppenburg, E.I. Rugarli, Astrocyte-specific deletion of the mitochondrial m-AAA protease reveals glial contribution to neurodegeneration, Glia 67 (2019) 1526–1541, https://doi.org/10.1002/glia.23626. PMID: 30989755.
[33] E. Goubert, Y. Mircheva, F.M. Lasorsa, C. Melon, E. Profilo, J. Sutera, H. Becq, F. Palmieri, L. Palmieri, L. Aniksztejn, F. Molinari, Inhibition of the mitochondrial glutamate carrier SLC25A22 in astrocytes leads to intracellular glutamate accumulation, Front. Cell. Neurosci. 11 (2017) 149, https://doi.org/10.3389/fncel.2017.00149. PMID: 28620281.
[34] M.Y. Al-Shorbagy, W. Wadie, D.M. El-Tanbouly, Trimetazidine modulates mitochondrial redox status and disrupted glutamate homeostasis in a rat model of epilepsy, Front. Pharmacol. 12 (2021) 735165, https://doi.org/10.3389/fphar.2021.735165. PMID: 34690772.
[35] V. Parpura, V. Grubisic, A. Verkhratsky, Ca(2+) sources for the exocytotic release of glutamate from astrocytes, Biochim. Biophys. Acta 1813 (2011) 984–991, https://doi.org/10.1016/j.bbamcr.2010.11.006. PMID: 21118669.
[36] A. Semyanov, Spatiotemporal pattern of calcium activity in astrocytic network, Cell Calcium 78 (2019) 15–25, https://doi.org/10.1016/j.ceca.2018.12.007. PMID: 30579813.
[37] N. Zhang, S. Ding, Imaging of mitochondrial and cytosolic Ca(2+) signals in cultured astrocytes, Curr Protoc Neurosci 82 (2) (2018) 29 1–2 29 11, https://doi.org/10.1002/cpns.42. PMID: 29357111.
[38] M. Gomez-Gonzalo, G. Losi, A. Chiavegato, M. Zonta, M. Cammarota, M. Brondi, F. Vetri, L. Uva, T. Pozzan, M. de Curtis, G.M. Ratto, G. Carmignoto, An excitatory loop with astrocytes contributes to drive neurons to seizure threshold, PLoS Biol. 8 (2010) e1000352, https://doi.org/10.1371/journal.pbio.1000352. PMID: 20405049.
[39] K. Heuser, C.G. Nome, K.H. Pettersen, K.S. Abjorsbraten, V. Jensen, W. Tang, R. Sprengel, E. Tauboll, E.A. Nagelhus, R. Enger, Ca2+ signals in astrocytes facilitate spread of epileptiform activity, Cerebr. Cortex 28 (2018) 4036–4048, https://doi.org/10.1093/cercor/bhy196. PMID: 30169757.
[40] C. Diaz Verdugo, S. Myren-Svelstad, E. Aydin, E. Van Hoeymissen, C. Deneubourg, S. Vanderhaeghe, J. Vancraeynest, R. Pelgrims, M.I. Cosacak, A. Muto, C. Kizil, K. Kawakami, N. Jurisch-Yaksi, E. Yaksi, Glia-neuron interactions underlie state transitions to generalized seizures, Nat. Commun. 10 (2019) 3830, https://doi.org/10.1038/s41467-019-11739-z. PMID: 31444362.
[41] K. Uchino, Y. Tanaka, W. Ikezawa, M. Deshimaru, K. Kubota, T. Watanabe, S. Katsurabayashi, K. Iwasaki, S. Hirose, Astrocyte Ca(2+) signaling is facilitated in Scn1a(+/-) mouse model of Dravet syndrome, Biochem. Biophys. Res. Commun. 643 (2023) 169–174, https://doi.org/10.1016/j.bbrc.2022.12.084. PMID: 36610382.
[42] R.C. Reyes, V. Parpura, Mitochondria modulate Ca2+-dependent glutamate release from rat cortical astrocytes, J. Neurosci. 28 (2008) 9682–9691, https://doi.org/10.1523/JNEUROSCI.3484-08.2008. PMID: 18815254.
[43] H. Zhang, Y. Lian, N.Y. Xie, Z, Ectopic expression of Miro 1 ameliorates seizures and inhibits hippocampal neurodegeneration in a mouse model of pilocarpine epilepsy, Biochem. Cell. Biol. 96 (2018) 468–474, https://doi.org/10.1139/bcb-2017-0102. PMID: 29365285.
[44] Y. Li, C. Wang, Y. Lian, H. Zhang, X. Meng, M. Yu, Y. Li, N. Xie, Role of the mitochondrial calcium uniporter in Mg(2+)-free-induced epileptic hippocampal neuronal apoptosis, Int. J. Neurosci. 130 (2020) 1024–1032, https://doi.org/10.1080/00207454.2020.1715978. PMID: 31933404.
[45] I. Fernandez-Gonzalez, E. Galea, Astrocyte strategies in the energy-efficient brain, Essays Biochem. 67 (2023) 3–16, https://doi.org/10.1042/EBC20220077. PMID: 36350053.
[46] J.V. Andersen, S.K. Christensen, E.W. Westi, M. Diaz-delCastillo, H. Tanila, A. Schousboe, B.I. Aldana, H.S. Waagepetersen, Deficient astrocyte metabolism impairs glutamine synthesis and neurotransmitter homeostasis in a mouse model of Alzheimer's disease, Neurobiol. Dis. 148 (2021) 105198, https://doi.org/10.1016/j.nbd.2020.105198. PMID: 33242587.
[47] A.R. Harders, C. Arend, S.C. Denieffe, J. Berger, R. Dringen, Endogenous energy stores maintain a high ATP concentration for hours in glucose-depleted cultured primary rat astrocytes, Neurochem. Res. (2023), https://doi.org/10.1007/s11064-023-03903-1. PMID: 36914795.

[48] H. Franke, A. Verkhratsky, G. Burnstock, P. Illes, Pathophysiology of astroglial purinergic signalling, Purinergic Signal. 8 (2012) 629–657, https://doi.org/10.1007/s11302-012-9300-0. PMID: 22544529.
[49] P.B. Guthrie, J. Knappenberger, M. Segal, M.V. Bennett, A.C. Charles, K. Sb, ATP released from astrocytes mediates glial calcium waves, J. Neurosci. 19 (1999) 520–528, https://doi.org/10.1523/JNEUROSCI.19-02-00520.1999. PMID: 9880572.
[50] E. Beamer, G. Conte, T. Engel, ATP release during seizures - a critical evaluation of the evidence, Brain Res. Bull. 151 (2019) 65–73, https://doi.org/10.1016/j.brainresbull.2018.12.021. PMID: 30660718.
[51] E. Beamer, M. Kuchukulla, D. Boison, T. Engel, ATP and adenosine-Two players in the control of seizures and epilepsy development, Prog. Neurobiol. 204 (2021) 102105, https://doi.org/10.1016/j.pneurobio.2021.102105. PMID: 34144123.
[52] Blauwblomme T. Dossi, J. Moulard, O. Chever, F. Vasile, E. Guinard, M. Le Bert, I. Couillin, J. Pallud, L. Capelle, G. Huberfeld, R. N, Pannexin-1 channels contribute to seizure generation in human epileptic brain tissue and in a mouse model of epilepsy, Sci. Transl. Med. 10 (2018) eaar3796, https://doi.org/10.1126/scitranslmed.aar3796. PMID: 29848662.
[53] C.G. Fonseca, C.R. Green, N. Lf, Upregulation in astrocytic connexin 43 gap junction levels may exacerbate generalized seizures in mesial temporal lobe epilepsy, Brain Res. 929 (2002) 105–116, https://doi.org/10.1016/s0006-8993(01)03289-9. PMID: 11852037.
[54] L. Walrave, A. Pierre, G. Albertini, N. Aourz, D. De Bundel, A. Van Eeckhaut, M. Vinken, C. Giaume, L. Leybaert, I. Smolders, Inhibition of astroglial connexin43 hemichannels with TAT-Gap19 exerts anticonvulsant effects in rodents, Glia 66 (2018) 1788–1804, https://doi.org/10.1002/glia.23341. PMID: 29683209.
[55] E.T. Chouchani, V.R. Pell, E. Gaude, D. Aksentijević, S.Y. Sundier, E.L. Robb, A. Logan, S.M. Nadtochiy, E.N.J. Ord, A.C. Smith, F. Eyassu, R. Shirley, C.H. Hu, A. J. Dare, A.M. James, S. Rogatti, R.C. Hartley, S. Eaton, A.S.H. Costa, P.S. Brookes, S.M. Davidson, M.R. Duchen, K. Saeb-Parsy, M.J. Shattock, A.J. Robinson, L. M. Work, C. Frezza, T. Krieg, M. Mp, Ischemic accumulation of succinate controls reperfusion injury through mitochondrial ROS, Nature 515 (2014) 431–435, https://doi.org/10.1038/nature13909. PMCID: PMC4255242.
[56] L.A. Volobouева, S.W. Suh, R.A. Swanson, R.G. Giffard, Inhibition of mitochondrial function in astrocytes: implications for neuroprotection, J. Neurochem. 102 (2007) 1383–1394, https://doi.org/10.1111/j.1471-4159.2007.04634.x. PMID: 17488276.
[57] J. Zhao, D. Qu, Z. Xi, Y. Huan, K. Zhang, C. Yu, D. Yang, J. Kang, W. Lin, S. Wu, Y. Wang, Mitochondria transplantation protects traumatic brain injury via promoting neuronal survival and astrocytic BDNF, Transl. Res. 235 (2021) 102–114, https://doi.org/10.1016/j.trsl.2021.03.017. PMID: 33798765.
[58] K. Hayakawa, E. Esposito, X. Wang, Y. Terasaki, Y. Liu, C. Xing, X. Ji, E.H. Lo, Transfer of mitochondria from astrocytes to neurons after stroke, Nature 535 (2016) 551–555, https://doi.org/10.1038/nature18928. PMID: 27466127.
[59] X.C. Ni, H.F. Wang, Y.Y. Cai, D. Yang, R.N. Alolga, B. Liu, J. Li, F.Q. Huang, Ginsenoside Rb1 inhibits astrocyte activation and promotes transfer of astrocytic mitochondria to neurons against ischemic stroke, Redox Biol. 54 (2022) 102363, https://doi.org/10.1016/j.redox.2022.102363. PMID: 35696763.
[60] C. Sun, X. Liu, B. Wang, Z. Wang, Y. Liu, C. Di, J. Si, H. Li, Q. Wu, D. Xu, J. Li, G. Li, Y. Wang, F. Wang, H. Zhang, Endocytosis-mediated mitochondrial transplantation: transferring normal human astrocytic mitochondria into glioma cells rescues aerobic respiration and enhances radiosensitivity, Theranostics 9 (2019) 3595–3607, https://doi.org/10.7150/thno.33100. PMID: 31281500.
[61] C. Chen, E. Mossman, P. Malko, D. McDonald, A.P. Blain, L. Bone, D. Erskine, A. Filby, A.E. Vincent, G. Hudson, A.K. Reeve, Astrocytic changes in mitochondrial oxidative phosphorylation protein levels in Parkinson's disease, Mov. Disord. 37 (2021) 302–314, https://doi.org/10.1002/mds.28849. PMID: 34779538.
[62] X.Y. Cheng, S. Biswas, J. Li, C.J. Mao, O. Chechneva, J. Chen, K. Li, J. Li, J.R. Zhang, C.F. Liu, W.B. Deng, Human iPSCs derived astrocytes rescue rotenone-induced mitochondrial dysfunction and dopaminergic neurodegeneration in vitro by donating functional mitochondria, Transl. Neurodegener. 9 (2020) 13, https://doi.org/10.1186/s40035-020-00190-6. PMID: 32345341.
[63] K. English, A. Shepherd, N.-E. Uzor, R. Trinh, A. Kavelaars, C.J. Heijnen, Astrocytes rescue neuronal health after cisplatin treatment through mitochondrial transfer, Acta Neuropathologica Communications 8 (2020), https://doi.org/10.1186/s40478-020-00897-7. PMID: 32197663.
[64] H. Wu, Y. Liu, H. Li, C. Du, K. Li, S. Dong, Q. Meng, H. Zhang, TRAK1-Mediated abnormality of mitochondrial fission increases seizure susceptibility in temporal lobe epilepsy, Mol. Neurobiol. 58 (2021) 1237–1247, https://doi.org/10.1007/s12035-020-02175-y. PMID: 33119838.
[65] K.A. Simeone, S.A. Matthews, K.K. Samson, T.A. Simeone, Targeting deficiencies in mitochondrial respiratory complex I and functional uncoupling exerts anti-seizure effects in a genetic model of temporal lobe epilepsy and in a model of acute temporal lobe seizures, Exp. Neurol. 251 (2014) 84–90, https://doi.org/10.1016/j.expneurol.2013.11.005. PMID: 24270080.
[66] B. Styr, N. Gonen, D. Zarhin, A. Ruggiero, R. Atsmon, N. Gazit, G. Braun, S. Frere, I. Vertkin, I. Shapira, M. Harel, L.R. Heim, M. Katsenelson, O. Rechnitz, S. Fadila, D. Derdikman, M. Rubinstein, T. Geiger, E. Ruppin, I. Slutsky, Mitochondrial regulation of the hippocampal firing rate set point and seizure susceptibility, Neuron 102 (2019) 1009–1024 e8, https://doi.org/10.1016/j.neuron.2019.03.045. PMID: 31047779.
[67] P. Lopriore, F. Gomes, V. Montano, G. Siciliano, M. Mancuso, Mitochondrial epilepsy, a challenge for neurologists, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms232113216. PMID: 36362003.
[68] S. Ponchaut, F.K. van Hoof, V, Cytochrome aa3 depletion is the cause of the deficient mitochondrial respiration induced by chronic valproate administration, Biochem. Pharmacol. 43 (1992) 644–647, https://doi.org/10.1016/0006-2952(92)90590-f. PMID: 1347214.
[69] J. Finsterer, Z.M. S, Mitochondrial toxicity of antiepileptic drugs and their tolerability in mitochondrial disorders, Expet Opin. Drug Metabol. Toxicol. 8 (2012) 71–79, https://doi.org/10.1517/17425255.2012.644535. PMID: 22149023.
[70] J.C. Chang, K.H. Liu, Y.C. Li, S.J. Kou, Y.H. Wei, C.S. Chuang, M. Hsieh, C.S. Liu, Functional recovery of human cells harbouring the mitochondrial DNA mutation MERRF A8344G via peptide-mediated mitochondrial delivery, Neurosignals 21 (2013) 160–173, https://doi.org/10.1159/000341981. PMID: 23006856.
[71] X. Jia, Q. Wang, J. Ji, W. Lu, Z. Liu, H. Tian, L. Guo, Y. Wang, Mitochondrial transplantation ameliorates hippocampal damage following status epilepticus, Animal Model Exp Med 6 (2023) 41–50, https://doi.org/10.1002/ame2.12310. PMID: 36734302.