



Energy metabolism in ALS: an underappreciated opportunity?

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Abstract

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive and fatal neurodegenerative disorder that primarily affects motor neurons. Despite our increased understanding of the genetic factors contributing to ALS, no effective treatment is available. A growing body of evidence shows disturbances in energy metabolism in ALS. Moreover, the remarkable vulnerability of motor neurons to ATP depletion has become increasingly clear. Here, we review metabolic alterations present in ALS patients and models, discuss the selective vulnerability of motor neurons to energetic stress, and provide an overview of tested and emerging metabolic approaches to treat ALS. We believe that a further understanding of the metabolic biology of ALS can lead to the identification of novel therapeutic targets.

Keywords Amyotrophic lateral sclerosis · Energy metabolism · Neuron-glia metabolic coupling · Mitochondria · Metabolic dysfunction · Metabolic treatment

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the selective and progressive degeneration of motor neurons in the brain and spinal cord. Motor neuron deterioration leads to muscle weakness and results in death due to respiratory failure typically within 3–5 years after diagnosis [25]. In the Western world, the lifetime risk of developing ALS is estimated to be 1 in 400 [89].

ALS is a highly heterogeneous disease [187]; 5–10% of patients have a familial form in which inheritance almost exclusively occurs via an autosomal dominant Mendelian pattern. While over 120 potential ALS genes (<http://alsod.iop.kcl.ac.uk/>) have been identified, more than half of familial ALS patients carry mutations in either ‘*superoxide dismutase 1*’ (SOD1), ‘*TAR DNA binding protein*’ (TARDBP), ‘*fused in sarcoma*’ (FUS), or carry a hexanucleotide

repeat expansion in an intronic region of the ‘*chromosome 9 open reading frame 72*’ (C9ORF72) gene [190]. Despite the genetic heterogeneity, most patients show cytoplasmic inclusions in motor neurons which stain positive for TDP-43, the protein product of *TARDBP* [136]. This suggests that similar pathogenic mechanisms may be present in different ALS subtypes. Although most ALS patients have no family history, unraveling the genetic basis of the disease led to an array of ALS models, put forth different processes believed to be involved in ALS pathogenesis, and led to various clinical trials [190]. Despite these efforts, translation of preclinical findings into effective therapeutic strategies remained poor. Riluzole and edaravone are the only FDA-approved drugs to treat ALS. Riluzole prolongs life by only a few months [12] and edaravone improves patient functionality scores in a subset of patients [165, 211]. Due to the unavailability of effective drugs, there is an urgent need for new treatment modalities in ALS.

A growing body of evidence shows dysregulated energy metabolism in ALS patients and models. Several of the metabolic abnormalities in ALS correlate to disease susceptibility and progression. Moreover, the remarkable vulnerability of motor neurons to energy depletion has become increasingly clear. In this review, we focus on how energy metabolism is impaired in ALS, and how motor neuron physiology contributes to their particular vulnerability to metabolic stress. We also discuss tested and emerging metabolism-centric therapeutic avenues for ALS.

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Systemic metabolism correlates to ALS disease course

Control of whole-body energy homeostasis, the balance between energy uptake and expenditure, is crucial to maintain stable body weight and hence overall health [105]. In ALS patients, energy homeostasis is imbalanced [57]. While energy uptake is often lowered [1], energy expenditure is suggested to be increased in a significant proportion of patients with ALS [21]. While this observation stems from predictive equations which still need validation in ALS patients and should, therefore, be interpreted with care [176], energy expenditure exceeds uptake in most ALS patients, leading to reduced fat depots [81]. Imbalanced energy homeostasis is also a consistent finding in different SOD1 [56, 62] and TDP-43 mouse models [30, 36]. Recently, the melanocortin pathway, a critical regulator of energy homeostasis and food intake in the hypothalamus [184], was hypothesized to contribute to imbalanced energy homeostasis in ALS patients [67] and mice [201]. However, reducing energy expenditure and inducing hyperphagia by targeting this pathway in mutant SOD1^{G93A} mice did not improve motor function or lifespan [53]. While the cause and importance of dysregulated energy homeostasis in human ALS remains to be established, body weight loss is an important prognostic factor in patients [149]. A lower pre-symptomatic body mass index has been reported in ALS patients [86, 126, 149] and the ALS risk is reduced up to 40% among obese individuals [138]. In agreement, increased prediagnostic body fat [65], subcutaneous fat [111], and serum leptin [135] were associated with a decreased risk of ALS mortality.

The majority of ALS patients suffer from hypolipidemia [215]. Of note, hypolipidemia is also present in mutant SOD1 mice [62, 98] and precedes clinical onset in mutant SOD1^{G93A} mice [98]. Whether hypolipidemia is also a pre-clinical feature in human ALS patients is difficult to assess, since diagnostic certainty is only reached in a progressed stage of the disease. In addition, elevated serum cholesterol and apolipoprotein E levels prolong survival and delay disease progression in ALS patients in most [52, 54, 103], but not all [31], studies, while statin treatment was associated with worsened outcome [224]. An additional study showed a positive correlation between blood lipids and respiratory function in ALS patients, potentially due to the decrease in CO₂ production, which lowers the load on ventilatory muscles [27, 31].

Interestingly, ALS patients suffering from diabetes show a delay in the onset of motor symptoms for up to 4 years [87]. A large case–control study reported an estimated odds ratio for ALS association with diabetes of 0.61 (95% confidence

interval: 0.46–0.80) [99]. Remarkably, type II diabetes was associated with a decreased risk of ALS (odds ratio 0.79, 95% confidence interval: 0.68–0.91) [127], while type I diabetes was associated with an increased risk (odds ratio 5.38, 95% confidence interval: 1.87–15.51) [194]. These data suggest that a potential protective effect is restricted to type II diabetes. Large longitudinal studies are required to determine whether insulin resistance (a hallmark of type II diabetes) per se has a protective effect against ALS or whether the protective effect is secondary to environmental and/or genetic factors that contribute to the development of type II diabetes. Moreover, ALS patients often develop insulin resistance during the course of the disease [154]. Since muscle tissue represents the major site of glucose consumption and storage, the development of insulin resistance during ALS is considered a consequence of muscle atrophy, although molecular evidence is still lacking. Even more, it has been suggested that deregulation of carbohydrate metabolism might contribute to ALS pathogenesis (see below).

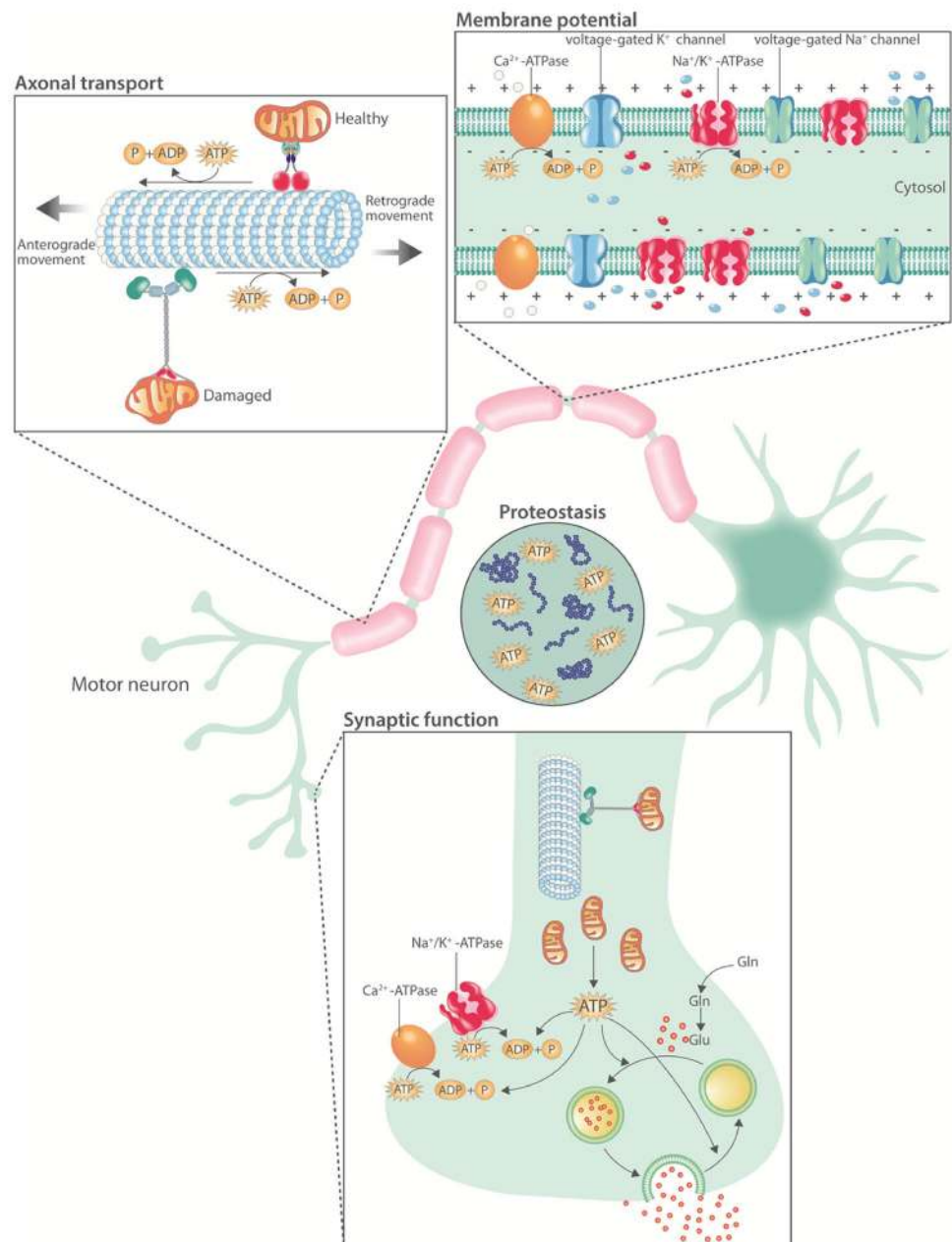
Altogether, systemic metabolic defects in ALS correlate with disease duration and/or progression [21, 26, 81]. However, it remains to be determined whether and how these defects are causally connected to ALS pathogenesis.

Motor neuron metabolism in health

Since its first description by Charcot in 1869, the characteristic selective degeneration and death of motor neurons in ALS has remained an enigma. Neurons are large, polarized, excitable cells and, therefore, face unique challenges to maintain energy homeostasis (Fig. 1). They are the main contributors to the impressive energy demand of the central nervous system (CNS). First, action potential propagation is highly dependent on the Na⁺/K⁺-ATPase [75]. Second, due to the extensive length of their neurites, neurons, and, a fortiori, motor neurons, depend on axonal transport [155]. Importantly, the molecular motors driving axonal transport hydrolyze one ATP molecule, generated via on-board glycolysis [217], for every 8-nm displacement of their cargo [79, 167]. Since synapses are major sites of neuronal energy consumption, the trafficking of mitochondria is critical to meet synaptic energy requirements [174]. On top of this, high ATP concentrations are needed to keep proteins soluble [143]. The high dependence of motor neurons on continuous energy provision to maintain their normal function and integrity renders them particularly vulnerable to energetic stress [106].

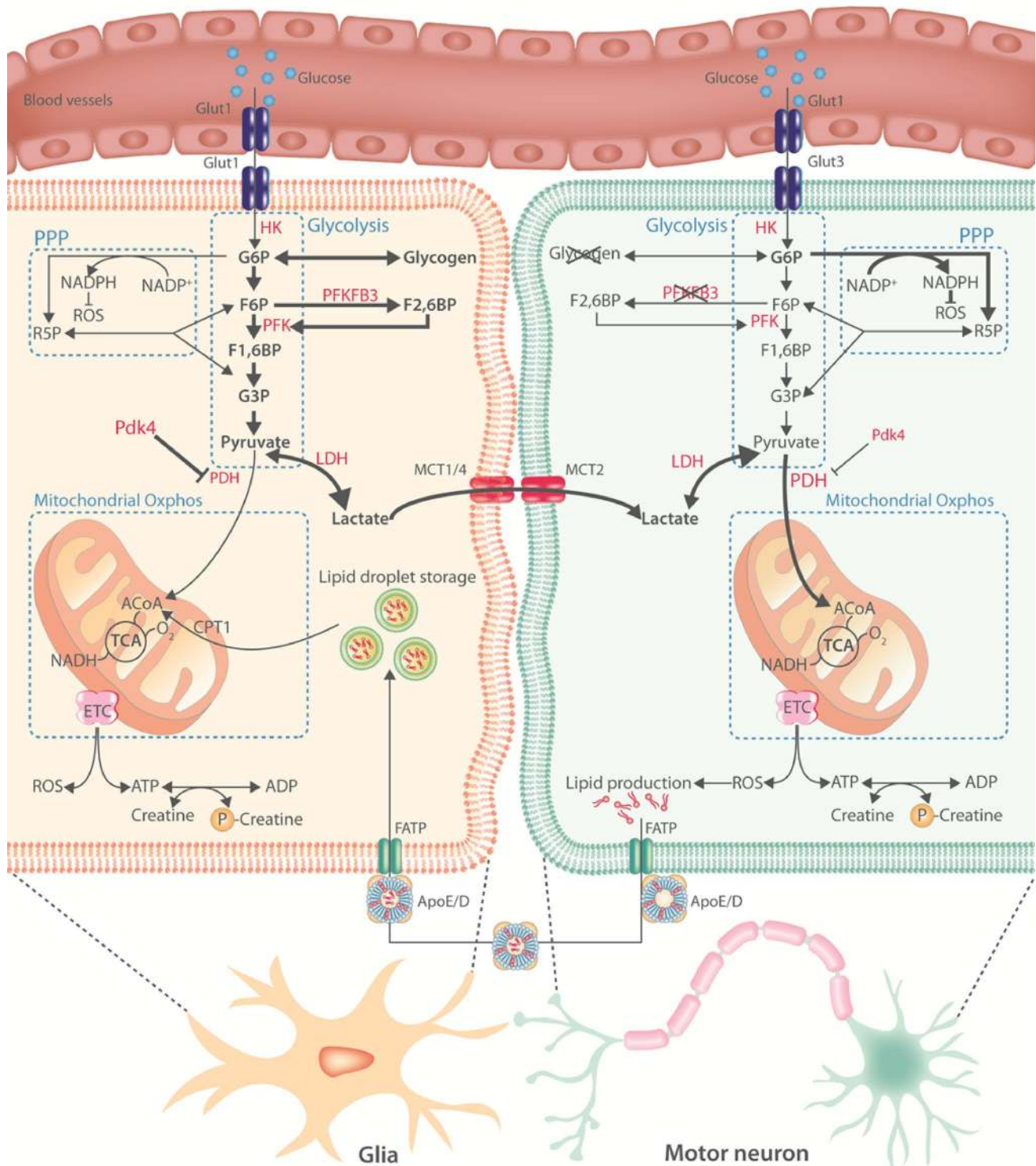
To meet its substantial energy demand, the CNS largely relies on glucose as an energy substrate [121]. Recent *in vitro* and *ex vivo* studies have indicated though that

Fig. 1 Overview of ATP consuming processes in motor neurons. Motor neuron physiology is highly energy demanding. First, the Na^+/K^+ -ATPase and the Ca^{2+} -ATPase hydrolyze ATP to establish and maintain the membrane potential and calcium homeostasis, respectively. Second, the molecular motors driving axonal transport depend on ATP hydrolysis. Third, synaptic activity is energetically expensive due to ion pumping, vesicular neurotransmitter uptake, and the endocytosis of vesicles from the synaptic cleft. Fourth, millimolar concentrations of ATP are required to maintain proteostasis. *Gln* glutamine, *Glu* glutamate, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *P* inorganic phosphate



neurons can readily oxidize several non-glucose substrates and that a switch towards glutamate oxidation could protect neurons from excitotoxic cell death [49, 61]. These data, nonetheless, require *in vivo* confirmation, since the absence of the blood–brain/spinal cord barrier and specific conditions of the CNS microenvironment might make it difficult to translate *in vitro* findings to an *in vivo* situation. Indeed, to date, the evidence indicates that only ketone bodies can sustain the energetic requirements of the CNS in conditions of severe glucose deprivation [35, 104]. Fatty acids are only poorly used as an energy substrate presumably due to:

the slow passage of fatty acids across the blood–brain and blood–spinal cord barrier, the higher oxygen cost of fatty acid oxidation, the elevated superoxide generation during fatty acid oxidation in combination with poor anti-oxidant defense mechanisms of neurons, and the slower rate of ATP generation of fatty acid oxidation [168]. More than 90% of ATP generation in the CNS occurs via mitochondrial oxidative phosphorylation [82]. Acute fluctuations in ATP demand in the CNS are met by the creatine/phosphocreatine system, which represents an instant way to liberate high-energy phosphates for ATP by the transphosphorylation of



phosphocreatine by creatine kinases [4]. Since ATP turnover in the CNS is high and substrate reserves small, the creatine/phosphocreatine system is crucial to buffer ATP fluctuations upon neuronal firing [16]. Moreover, the faster diffusion rate of phosphocreatine compared to ATP, and creatine compared

to ADP [200], makes the creatine/phosphocreatine system suitable to connect sites of ATP generation to sites of ATP consumption.

Despite glucose being the dominant energy substrate, the CNS is a highly heterogeneous tissue composed of different

Fig. 2 Motor neuron metabolism in health. An overview of the current knowledge on motor neuron energy metabolism. Metabolic pathways are indicated in blue, important enzymes in red. Bold black arrows indicate the main metabolic routes in glia or motor neurons. Neurons have low glycogen stores and low expression and activity of PFKFB3. Activity of PDH is higher in neurons compared to glia. These differences result in a predominantly oxidative versus glycolytic metabolic profile in neurons and glia, respectively. According to the astrocyte-neuronal lactate shuttle hypothesis, glia-derived lactate is shunted to motor neurons where it undergoes oxidative phosphorylation. ROS generation in motor neurons promotes lipid production. These lipids are transported to glia where they can be stored or catabolized. *Glut* glucose transporter, *HK* hexokinase, *G6P* glucose 6-phosphate, *R5P* ribose 5-phosphate, *F6P* fructose 6-phosphate, *PFK* phosphofructokinase, *PFKFB3* phosphofructokinase-2/fructose-2,6-bisphosphatase, *F1,6BP* fructose 1,6-bisphosphate, *NADP⁺* oxidized nicotinamide adenine dinucleotide phosphate, *NADPH* reduced nicotinamide adenine dinucleotide phosphate, *ROS* reactive oxygen species, *G3P* glyceraldehyde 3-phosphate, *LDH* lactate dehydrogenase, *PDH* pyruvate dehydrogenase, *Pdk4* pyruvate dehydrogenase kinase 4, *Oxphos* oxidative phosphorylation, *MCT* monocarboxylate transporter, *ACoA* acetyl coenzyme A, *CPT1* carnitine palmitoyltransferase 1, *TCA* tricarboxylic acid cycle, *O₂* molecular oxygen, *NADH* reduced nicotinamide adenine dinucleotide, *ETC* electron transport chain, *FATP* fatty acid transport protein, *APOE/D* apolipoprotein E/D, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate

cell types which show distinct metabolic profiles (Fig. 2). Differences are mainly studied in neurons and astrocytes, and indicate that neurons are predominantly oxidative and that astrocytes are predominantly glycolytic [22, 121, 219]. Under normal conditions, carbohydrate catabolism comprises the conversion of glucose to pyruvate via glycolysis followed by the full oxidation of glucose, or its metabolites pyruvate or lactate, in the mitochondria by the tricarboxylic acid (TCA) cycle and electron transport chain. Oxidative catabolism requires oxygen and generates 31–36 molecules of ATP for every molecule of glucose (or half of it if lactate or pyruvate is used as substrate). However, when the availability of oxygen is low (or in specific cell types—see below), glucose is only glycolytically catabolized to pyruvate, which generates only two molecules of ATP for each molecule of glucose, and is subsequently converted to lactate. This is a necessary step, since the regeneration of nicotinamide-adenine dinucleotide (NAD⁺) is required to keep glycolysis going when oxygen is limited [116]. Pyruvate dehydrogenase (PDH) is crucial to allow pyruvate entry into the TCA cycle and, hence, controls oxidative versus anaerobic catabolism. In astrocytes, PDH activity is low compared to neurons [73]; and pyruvate dehydrogenase kinase 4 expression, the main kinase suppressing PDH activity, is high, leading to higher glycolysis and lactate production [219]. In contrast, neurons have a lower rate of glycolysis under normal conditions due to the constant degradation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), a key positive modulator of glycolysis, by the E3 ubiquitin ligase anaphase-promoting complex/cyclosome

[18, 78]. In agreement, glia transport and metabolize glucose analogues faster than neurons both *ex vivo* [9] and *in vivo* [85]. In addition, a part of the glucose that is taken up by neurons does not enter glycolysis but is instead directed to the pentose phosphate pathway (PPP) during which the antioxidant reduced glutathione is regenerated (Fig. 2). Both overexpression [78] and stabilization [158] of PFKFB3 in neurons activated glycolysis at the expense of the PPP and resulted in oxidative stress and apoptotic death. These data suggest that neuronal homeostasis is particularly dependent on a tight balance between glycolysis and PPP flux to ensure sufficient ATP production while maintaining anti-oxidant status.

The more oxidative profile of neurons and more glycolytic profile of glia becomes more pronounced upon neuronal activity [76, 124], suggesting that other energy substrates are used to meet the neuronal energy demand during neuronal activity. Lactate is consumed in an activity-dependent manner in the CNS [162, 212] and is mainly oxidized by neurons compared to astrocytes [20, 196]. According to the astrocyte-neuronal lactate shuttle hypothesis, lactate is provided to neurons by astrocytes [147]. In brief, the reuptake of glutamate by astrocytes depletes their ATP stores, which stimulates the uptake of glucose and subsequently the glycolytic flux. The resulting lactate is mainly exported through the astrocyte-specific monocarboxylate transporter 4 (MCT4) and taken up by the neuron-specific MCT2 transporters. Next, it is fully oxidized to generate ATP (for a review, see [121]). In addition to lactate, astrocytes can also provide pyruvate and ketone bodies to the neurons [148]. Oxidative phosphorylation of glia-derived substrates in neurons leads to the generation of reactive oxygen species (ROS) which promote lipid production [112, 113]. Those lipids are transported to astrocytes via a fatty acid transport proteins (FATP) and apolipoprotein-dependent mechanism where they can form lipid droplets, be shunted into the ketogenic pathway, or undergo fatty acid oxidation [71] (Fig. 2). Impaired transport of lipids from neurons to glia accelerates neurodegeneration [112], suggesting a pro-survival function of neuron-derived lipids in glia by serving as *in situ* energy substrates under stress. Of note, while astrocyte-neuron metabolic coupling seems to be essential for nervous system homeostasis in *Drosophila* [204] and mice [64, 109, 120], it does not imply a complete metabolic compartmentalization of glycolysis versus oxidative phosphorylation in glia and neurons, respectively [7, 48]. Indeed, neurons also take up and metabolize glucose and increase glucose consumption in an activity-dependent manner [6, 47, 144]. In addition, neurons can catabolize glucose and lactate at the same time [115]. Therefore, it is likely that both oxidative phosphorylation of glia-derived energy substrates as well as neuronal glycolysis contribute to ATP production in high-energy demanding cellular situations.

Astrocyte contact with neurons is generally limited to the neuronal soma, synapses, and nodes of Ranvier, leaving the largest part of the axon without metabolic support from astrocytes. This is especially true for motor neurons. In contrast, oligodendrocytes are well connected to the axon and perfectly positioned to support the metabolic demands of neurons [151]. These glial cells highly express MCT1, which is the MCT with the highest affinity for lactate [152]. MCT1 inhibition in organotypic spinal cord slice cultures reduced motor neuron survival, but this effect was rescued by the addition of high concentrations of lactate to the culture medium [109], suggesting that oligodendrocyte-derived lactate contributes to the survival of motor neurons. In addition, astrocyte-to-oligodendrocyte coupling is essential for myelination [193]. Whether coupling between different glial cells is also involved in the metabolic support of motor neurons is unknown.

In summary, motor neurons require vast amounts of energy while having limited energy stores. Therefore, neuronal function and survival requires the continuous provision of substantial amounts of nutrients for ATP production. Under normal conditions, neurons are predominantly oxidative and astrocytes are predominantly glycolytic [219]. In addition, neurons keep a tight balance between glycolysis and flux through the PPP to maintain their anti-oxidant status while ensuring optimal ATP production. Of note, the metabolic characteristics of neurons have been studied to a large extent in cortical neurons. Whether and how motor neurons, due to their specific anatomy and microenvironment, have different metabolic properties, remain to be determined. Their high need for continuous energy provision, nonetheless, renders motor neurons particularly vulnerable to energetic stress [106]; and this could contribute to the selective vulnerability and degeneration of motor neurons observed in ALS. Indeed, fast-fatigable motor neurons, which have the highest peak needs of ATP [106], are initially targeted and are more severely affected during ALS compared to slow motor neurons [137].

Motor neuron metabolism in ALS

Cellular energy homeostasis is impaired in ALS

Mammalian AMP-activated protein kinase (AMPK) is a major cellular energy sensor activated by falling energy status. Upon activation, AMPK restores energy homeostasis by promoting catabolic pathways, resulting in ATP generation, and inhibiting anabolic pathways that consume ATP [74]. Enhanced AMPK activation was observed in motor neurons of ALS patients and correlated closely with the extent of cytoplasmic mislocalization of TDP-43 [114]. In NSC34 motor neuron-like cells,

5-aminoimidazole-4-carboxamide-1- β -*d*-ribofuranoside (AICAR)-mediated activation of AMPK caused TDP-43 mislocalization [114]. These data link energy depletion in human motor neurons to ALS-related TDP-43 pathology. AMPK activation was also increased in spinal cord cultures or lysates of mutant SOD1^{G93A} mice [110]. Pharmacological activation of AMPK worsened disease outcome in these mice [91]. In accordance, reducing AMPK-activity improved disease outcome in vitro or in *C. elegans* models expressing mutant SOD1 or TDP-43 [110]. These studies collectively show disturbed energy homeostasis at the cellular level in ALS and demonstrate its role in TDP-43 proteinopathy, the histopathological signature of ALS. While a clear mechanistic link between AMPK activation and TDP-43 mislocalization is currently lacking, nucleocytoplasmic transport is known to be an energy-dependent process [17]. It is, therefore, possible that cytoplasmic mislocalization of an aggregation prone protein such as TDP-43 [88] results from AMPK-mediated inhibition of nucleocytoplasmic transport.

Mitochondrial dysfunction, an ALS hallmark

Mitochondrial dysfunction is a clinical hallmark of both sporadic and familial ALS [23, 55, 163]. As a consequence, multiple processes in which mitochondria play a key role are extensively investigated in ALS [182]. Seminal studies have shown dense clusters of mitochondria in the anterior horn of the lumbar spinal cord [164] and presynaptic mitochondrial swelling in motor neurons [180] of ALS patients. In addition, the amount of mitochondrial DNA, a direct marker of mitochondrial abundance, was reduced in the spinal cord from familial and sporadic ALS patients [207]. In mice carrying the SOD1^{G37R} mutation, membrane-bound vacuoles derived from degenerating mitochondria were observed in neurites [210]. Massive mitochondrial degeneration in motor neurons of mutant SOD1^{G93A} mice was already observed at disease onset [41, 102]. The observation that mitochondrial morphology is also abnormal in various murine FUS [80, 183] and TDP-43 models [170, 213] is important, since overexpression of human SOD1 per se, rather than the pathogenic effect of the mutation, induces mitochondrial vacuolization [84]. Besides morphological abnormalities, functional changes are present in ALS mitochondria. In spinal cord mitochondria from ALS patients, there was decreased activity of the electron transport chain (ETC) complexes I + III, II + III, and IV [207]. Decreased activity of the mitochondrial enzymes citrate synthase and cytochrome c oxidase was also reported in motor neurons from ALS patients [19]. Furthermore, impaired activities of complex I + III, II + III, and IV were also observed in mutant SOD1^{G93A} mice [129]. Importantly, reduced respiration and ATP synthesis preceded behavioral deficits in mutant SOD1^{G93A} mice [90,

[129, 188], indicating a role in pathology. This has not yet been validated in other ALS models.

In addition to abnormal mitochondrial morphology and function, the cellular distribution of mitochondria is altered in ALS. In ALS patients, mitochondrial accumulation was observed in the cell body and proximal axon hillock [163]. Disturbed mitochondrial dynamics were also observed in embryonic and adult motor neurons expressing mutant SOD1^{G93A} [15, 45, 185], mutant TDP-43 overexpressing mice [122], and FUS patient-derived motor neurons [70]. Expressing mutant TDP-43 in motor neurons also induced aberrant mitochondrial distribution [205]. Miro1, a mitochondrial outer membrane protein coupling mitochondria to the axonal transport machinery, is downregulated in ALS, suggesting a mechanistic basis for impaired mitochondrial distribution in ALS [134, 218].

Abnormal mitochondrial physiology is a consistent observation in ALS patients and in multiple ALS models (Fig. 3). In mutant SOD1 [90, 129, 188] and FUS [183] ALS mouse models, mitochondrial dysfunction is an early event and overexpressing peroxisome proliferator activated receptor- γ coactivator 1 alpha (PGC1 α), a major regulator of mitochondrial biogenesis, improved survival, motor function, and motor neuron survival in mutant SOD1^{G93A} mice [221]. PGC1 α expression is also downregulated in the CNS of FUS-ALS mice and FUS patient derived motor neurons [10]. Therefore, improving mitochondrial biogenesis may be an attractive therapeutic strategy for ALS. It should be noted that mitochondrial abnormalities in ALS are not restricted to motor neurons. In skeletal muscle from patients, mitochondria are also structurally [130, 203] and functionally [38, 58] abnormal. While alterations in skeletal muscle can affect neuromuscular junction integrity [209], their role in ALS remains controversial (for a review, see [117]).

This said, the underlying cause of mitochondrial dysfunction in ALS and whether mitochondrial dysfunction is causally linked to motor neuron pathology in ALS still remains an open question. It is also not yet clear whether mitochondrial defects are present in all ALS subtypes. Moreover, mechanisms linking mutations in TDP-43 and FUS to aberrant mitochondrial physiology remain to be determined. Overall, the current literature suggests that aberrant mitochondrial physiology could be an important contributing factor to the pathogenesis of ALS.

Carbohydrate metabolism and ALS

In line with mitochondrial dysfunction, glucose uptake in the motor-sensory cortex of ALS patients is reduced [77, 140]. FDG-PET studies linked the reduction of glucose uptake and phosphorylation to the severity of the disease [42]. Another FDG-PET study consisting of 81 patients with a suspected diagnosis of ALS was able to correctly classify

95% of ALS cases, indicating reduced glucose uptake as an early diagnostic event in ALS [197]. In mutant SOD1^{G93A} mice, glucose uptake in the spinal cord increased pre-symptomatically, but declined progressively during disease progression [133]. Under physiological conditions, there is a tight coupling between blood flow and glucose metabolism in the CNS [66]. Remarkably, the pre-symptomatic increase in glucose uptake in the spinal cord of mutant SOD1^{G93A} mice was not matched by increases in spinal blood flow [133]. Despite reduced glucose uptake, the spinal cord from end-stage mutant SOD1^{G93A} mice, as well as from autopsied ALS patients, is characterized by elevated concentrations of glycogen [50]. Blood flow–metabolism uncoupling together with increased glycogen storage in the CNS suggests a decreased ability to catabolize carbohydrates in mutant SOD1^{G93A} mice. However, it is debated whether reduced glucose uptake in the CNS of ALS patients reflects a reduction in neuronal carbohydrate catabolism or a reduction in the number of motor neurons. Nevertheless, the ability to catabolize carbohydrates appears to be reduced in human ALS patients as the expression of phosphoglucomutase 2 like 1 and phosphoglycerate kinase, two key enzymes in glycolysis, is downregulated in fibroblasts from sporadic ALS patients [157]. In agreement, a recent proteomic study in sporadic ALS skin fibroblasts showed a marked reduction in components of glycolysis [188]. Whole-genome expression profiling in the motor cortex of sporadic ALS patients also showed a significant downregulation of glycolytic genes [108]. Another study in *post-mortem* cortex of ALS patients identified an over twofold reduction in PFKFB3 mRNA content [206]. In contrast, introducing mutant SOD1 in human fibroblasts or NSC34 motor neuron-like cells increased glycolysis and reduced mitochondrial ATP generation [3, 195]. Given the limited capacity of neurons to upregulate glycolysis [78, 158], the physiological relevance to ALS of the upregulation of glycolysis in these cells remains to be established. Nevertheless, neurons can upregulate glycolysis [47] and oxidative stress is evident in *post-mortem* samples of ALS patients [63]. It is, therefore, possible that during severe energetic stress, motor neurons sacrifice their redox status to alleviate energetic stress and eventually die due to excessive oxidative stress.

It remains to be determined whether these metabolic alterations are taking place in motor neurons or glia (Fig. 3). Given that in both the cortex and the spinal cord, motor neurons represent a quantitatively minor population, functional metabolic studies on induced pluripotent stem cell (iPSC)-derived motor neurons from patients could provide valuable insight. Compared to neurons, glia are more glycolytic, and, therefore, likely significantly contribute to the observed reductions in transcription level of key glycolytic transcripts in the CNS of ALS patients. In oligodendrocytes from ALS patient and mutant SOD1^{G93A} mice, the expression of MCT1

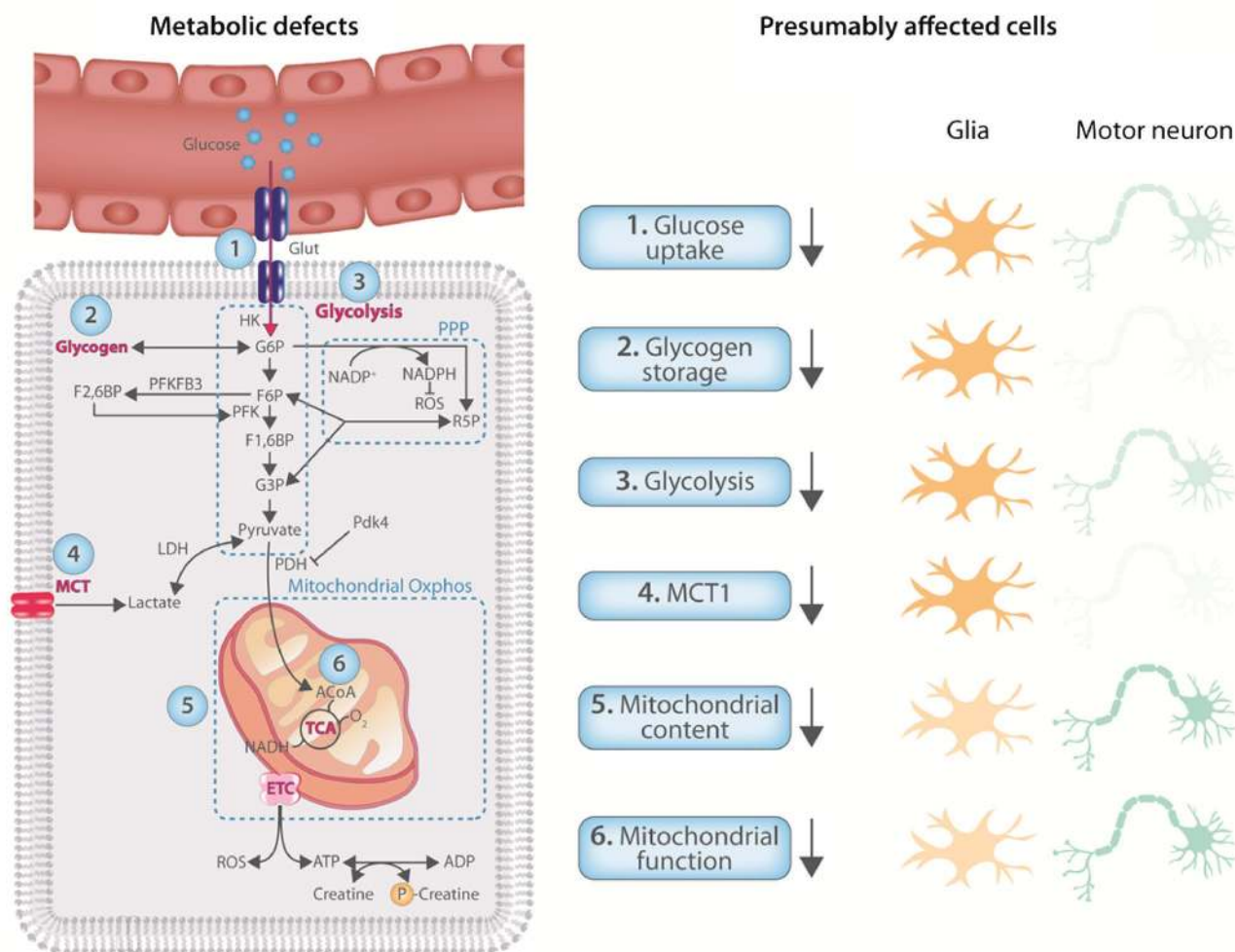


Fig. 3 CNS energy metabolism is dysregulated in ALS. Metabolic processes shown to be affected in the CNS of ALS patients and/or models. Although most defects have not been attributed to a specific

cell type, they are likely to result from either glia or motor neurons, or both. On the right, the presumably affected cell type(s) is/(are) colored darker

transporters is downregulated [92, 109, 150]. In addition, the downregulation of the glutamate transporter GLT-1 in astrocytes from ALS patients is well established [161]. These observations suggest that the reduced glycolytic capacity is, at least in part, due to changes in glial metabolism.

Taken together, reductions in glucose uptake and increased glycogen storage in the CNS of ALS patients and ALS animal models suggest a reduced capacity to catabolize glucose. Noteworthy, riluzole enhanced CNS glucose uptake both in vitro [43] and in vivo [32], suggesting that improving glucose transport rates in ALS affected cells may be a potential therapeutic avenue. While studies evaluating specific pathways are scarce, glycolysis seems to be downregulated. How different cell types in the CNS contribute to reduced carbohydrate catabolism remains to be investigated. Therefore, future studies investigating the metabolic fate of glucose, using, i.e., traceable glucose analogues [8],

in ALS models are urgently needed. Moreover, it is not clear how reduced carbohydrate catabolism might affect neuronal function.

Metabolic treatments tested in ALS

Energy metabolism is altered in ALS (Fig. 3) and correlates to disease progression, suggesting a role for energy metabolism in ALS pathogenesis. As a consequence, targeting metabolism represents a rational strategy to treat ALS. Below, we will give an overview of therapeutic approaches that target energy metabolism and have been tested in ALS patients and/or preclinical models (for an overview, see Table 1). Most approaches focus on increasing the provision of energetic substrates or improving mitochondrial function. Some strategies target the electron transport chain as the

most important cellular source of oxidative stress. Creatine has also been investigated for its energy buffering capacities. Of note, most metabolic treatments have multiple mechanisms of action. One example is dichloroacetate, which improves mitochondrial function indirectly by stimulating the conversion of pyruvate to acetyl coenzyme A (ACoA), and, therefore, also provides additional energy substrates to the TCA cycle. For reasons of clarity, we classified treatments according to their principal mechanism of action.

Creatine

As described above, the creatine/phosphocreatine system plays a crucial role in neurons for cellular energy buffering and transport [4]. In mutant *SOD1*^{G93A} mice, creatine treatment prevented ATP depletion in the cerebellar cortex and spinal cord [26], but not in skeletal muscle [46]. Creatine treatment in mutant *SOD1*^{G93A} mice markedly improved motor neuron survival but only moderately enhanced motor function and lifespan [101]. No studies evaluated the effect of creatine in other ALS mouse models. In ALS patients, creatine supplementation did not affect survival or disease progression [69, 160, 173]. Several reasons can explain the different effect of creatine in mutant *SOD1*^{G93A} mice and ALS patients. First, the efficacy of creatine in mutant *SOD1*^{G93A} mice can, at least in part, be explained by a buffering effect of creatine on *SOD1* overexpression-related mitochondriopathy [13, 84]. In addition, the treatment was initiated at different disease stages in mice compared to patients. While creatine intake in mutant *SOD1*^{G93A} mice was started before symptom onset and before the reduction in ATP concentration in the CNS [26], ALS patients' treatment started at least 1 year after symptom onset when already extensive alterations in energy metabolism are present. While creatine supplementation is able to prevent neuronal ATP depletion in some conditions and for short periods of time [186], it acts by energy buffering and transport without contributing to ATP production [4]. Therefore, it is likely that when treatment only commences during progressed disease states, the cascade of metabolic dysfunction is too far advanced for interventions to be successful.

Targeting oxidative stress

The interest in the role of oxidative stress was nurtured for decades by the finding that mutations in *SOD1* can cause ALS [159]. Whether oxidative stress is a primary or secondary disease mechanism in human ALS is still unclear. The recent discovery that the free radical scavenger edaravone improves ALS functional rating scale (ALSFRS) scores of

a subgroup of ALS patients suggests that oxidative stress affects motor neuron death [211]. Nevertheless, most clinical trials targeting oxidative stress failed to demonstrate clinical efficacy (see below). Given the vulnerability of motor neurons to oxidative stress [172], neurons employ different strategies to minimize ROS accumulation [168]. Hence, oxidative stress might be an indicator of advanced cellular damage rather than an early pathological event. Identifying the exact underlying mechanism responsible for the efficacy of edaravone in ALS patient subpopulations could provide further insight in the role of oxidative stress in ALS.

Coenzyme Q10 and MitoQ

Coenzyme Q, also known as ubiquinone, is the only endogenous lipid-soluble anti-oxidant found in humans. It acts as an essential cofactor in the electron transport chain where it accepts electrons from complex I and II and shuttles them to complex III. Its quinone group can be reduced to quinol, explaining its anti-oxidative properties [37]. In mutant *SOD1*^{G93A} mice, coenzyme Q10 induced a mild improvement in survival [128]. However, a phase II clinical trial, treating ALS patients with small amounts of coenzyme Q10 for 9 months, did not observe improvements on ALSFRS [95]. Of note, the feeding regimen in this study only induced a moderate increase in plasma coenzyme Q10 levels and the previous studies in Parkinson's disease suggest that doses up to 100-fold of the dose used are needed to slow disease progression [178, 179]. Although administration of high doses of exogenous coenzyme Q10 is well tolerated in humans [178], its hydrophobicity compromises bioavailability [128]. To improve this, MitoQ, a mitochondrion-targeted and recyclable coenzyme Q10 analogue, was developed [96]. MitoQ showed enhanced bioavailability and improved mitochondrial function in different neuronal cell types exposed to oxidative stress [189]. Rat mutant *SOD1*^{G93A} astrocytes were previously shown to be toxic to wild-type motor neurons [72, 214]. Interestingly, pretreatment of mutant *SOD1*^{G93A} astrocytes with low doses of MitoQ reduced oxidative damage and enhanced mitochondrial ATP generation in motor neurons [29]. Adding MitoQ to the drinking water of mutant *SOD1*^{G93A} mice slowed the decline of mitochondrial function in spinal cord and muscle, reduced spinal cord oxidative damage, improved the integrity of neuromuscular junctions, increased hindlimb strength, and prolonged the life span of mutant *SOD1*^{G93A} mice [132]. While these results are promising, no clinical trials assessed the efficacy or tolerability of MitoQ in ALS patients thus far.

Table 1 Metabolic treatments tested in ALS

Putative mechanism of action	Metabolic treatment	Effect on ALS models	Effect on ALS patients
Energy buffering and transport	Creatine	Improved lifespan, motor neuron survival, and motor function in mutant SOD1 ^{G93A} mice [87]	No efficacy in phase II/III clinical trials [55, 139, 151]
Oxidative stress	Coenzyme Q10	Improved survival in mutant SOD1 ^{G93A} mice—[111]	No efficacy in phase II clinical trial [81]
	MitoQ	Reduced toxicity of mutant SOD1 ^{G93A} rat astrocytes to healthy motor neurons in co-culture [24] Improved motor function, survival, and histopathology in mutant SOD1 ^{G93A} mice [114]	To be tested
	Dexpramipexole	Improved survival, and motor function in mutant SOD1 ^{G93A} mice in one study [36], but not in a second study [177] No effect in patient derived iPSCs [189] No effect in rat cortical neurons transfected with mutant or wild-type TDP-43 [177]	No efficacy in phase III clinical trial [33]
	Edaravone	Delayed motor neuron degeneration and spinal cord SOD1 deposition in mutant SOD1 ^{G93A} mice [71] Delayed disease progression in wobbler mice [69] Improved motor performance in mutant SOD1 ^{H46R} rats [5]	Efficacy in a subset of ALS patients [184], FDA-approved
Additional and/or alternative fuel	High caloric diet	Delayed disease onset and extended survival in mutant SOD1 ^{G93A} , mutant SOD1 ^{G86R} , and mutant TDP-43 ^{A315T} mice [30, 46] Delayed motor neuron loss in the spinal cord of mutant SOD1 ^{G93A} mice [46]	Promising results in a phase II clinical trial [182]
	Ketone bodies	Ketogenic diets delay disease onset, improved motor neuron survival but not lifespan in mutant SOD1 ^{G93A} mice [195] Ketone esters are to be tested in ALS models	To be tested
	Medium-chain triglycerides	Delayed disease onset, and improved motor neuron survival in mutant SOD1 ^{G93A} mice [167, 193]	To be tested
	Pyruvate	Improved motor performance, disease progression, and lifespan in mutant SOD1 ^{G93A} mice [121] but not in a subsequent study [48]	To be tested
Mitochondrial function	Dichloroacetate	Improved survival, delayed disease onset, and improved motor neuron survival in mutant SOD1 ^{G93A} mice [113, 120]	To be tested
	Acetyl-L-carnitine	Neurotrophic effects in rat embryonic motor neurons [10] Improved survival in mutant SOD1 ^{G93A} mice [86]	Promising results in a phase II clinical trial [8]

Dexpramipexole

Pramipexole is a dopamine agonist approved to treat Parkinson's disease [171] and restless leg syndrome [125]. In addition, pramipexole demonstrates anti-oxidative properties [107]. Dexpramipexole, the R+ enantiomer of pramipexole, has a 100-fold lower affinity for dopamine receptors than pramipexole, but is equipotent to scavenge ROS [44, 68]. Dexpramipexole improved metabolic efficiency, defined as the amount of ATP generated for a given value of oxygen consumption, in whole rat brain-derived mitochondria [2]. In mutant SOD1^{G93A} mice, dexpramipexole prolonged survival and delayed motor deterioration [44]. In a phase II clinical trial, dexpramipexole administration to ALS patients was well tolerated and tended to attenuate functional decline in a dose-dependent manner [39]. However, dexpramipexole did not differ from placebo for any efficacy measurement in a subsequent phase III clinical trial [40]. Moreover, dexpramipexole did not show a protective effect in subsequent preclinical studies in mutant SOD1^{G93A} mice [202], ALS patient derived iPSCs [216], or rat cortical neurons transfected with mutant or wild-type human TDP-43 [202].

Fueling energy metabolism

Imbalanced energy homeostasis is an early and persistent observation throughout the course of ALS. Moreover, endogenous energy stores, which are mainly located in skeletal muscle and adipose tissue, are progressively depleted during disease progression. Providing additional energetic substrates may, therefore, improve the clinical outcome. In addition, impairments in carbohydrate metabolism suggest that energy substrates other than glucose might have more pronounced effects. Enhancing the availability of specific metabolites is an alternative way to improve ATP production. This could be particularly important in neurons to compensate for losses of the TCA intermediate α -ketoglutarate that occur through the release of the α -ketoglutarate-derived neurotransmitters glutamate and GABA [169].

High caloric diets to treat ALS

In mutant SOD1^{G93A}, SOD1^{G86R}, and TDP43^{A315T} overexpressing mice [36, 56], a high fat diet delayed disease onset and extended survival, while caloric restriction shortened the lifespan of mutant SOD1^{G93A} mice [145, 146]. Moreover, a high fat diet attenuated motor neuron loss in the spinal cord of mutant SOD1^{G93A} mice [56]. A small prospective study in ALS patients showed that high caloric diets were able to abolish weight loss [51]. In a phase II clinical trial involving 20 patients, subjects were assigned to one of three diets using gastrostomy: caloric intake designed to

match caloric expenditure, a high fat diet, or a high carbohydrate diet both providing an excess of calories. One out of 17 patients assigned to a hypercaloric diet died during the 5-month follow-up period compared with three out of seven patients assigned to the control group [208]. While this study was promising, a sufficiently powered phase III clinical trial to examine the effect of hypercaloric diets on survival and functional outcome in ALS patients is still lacking. Moreover, whether the composition of the hypercaloric diet matters is an outstanding question.

Ketone bodies, ketogenic diets, and beyond

Ketone bodies are energy substrates endogenously produced from fat when glucose availability is limited. While the liver is the major site of ketogenesis, glial cells are also able to produce ketone bodies [5]. Ketone bodies have a high metabolic efficiency generating 30% more energy per molecule oxygen than pyruvate [199]. Therefore, ketones are suited to meet high-energy demands. Besides being an energy substrate, ketone bodies are signaling metabolites acting as histone deacetylase inhibitors to reduce oxidative stress [177]. In mutant SOD1^{G93A} mice, a ketogenic diet delayed disease onset and improved motor neuron survival without affecting lifespan [222]. However, as ketogenic diets are associated with a loss of muscle mass [24], the potential beneficial effect of ketosis on lifespan may be blunted. Recently, ketone esters have emerged as a novel approach to raise blood ketone bodies immediately [34, 97], even when co-ingesting high amounts of carbohydrates and proteins [198]. Ketone esters have improved disease outcome in an Alzheimer's disease mouse model [93]. In ALS, the therapeutic potential of ketone esters is unexplored.

Medium-chain triglycerides

Medium-chain triglycerides were previously used as a more palatable alternative to ketogenic diets to treat epilepsy and Alzheimer's disease [181]. Medium-chain triglycerides are able to cross the blood–brain barrier via diffusion and enter neurons via monocarboxylate transporters [168] where they can undergo β -oxidation to form ACoA and ketone bodies, which fuel the TCA cycle [192]. Two medium-chain triglycerides investigated in the context of ALS are caprylic triglyceride and triheptanoin, the triglycerides of octanoic acid (8C fatty acid) and heptanoic acid (7C fatty acid), respectively. Early administration of caprylic triglyceride to mutant SOD1^{G93A} mice delayed disease onset, improved motor performance, reduced motor neuron loss, and promoted mitochondrial oxygen consumption in the spinal cord [220]. Pre-symptomatic triheptanoin ingestion also delayed disease onset and reduced motor neuron loss at symptom onset in mutant SOD1^{G93A} mice [191]. Clinical trials

evaluating safety or efficacy of medium-chain triglyceride treatments in ALS patients are lacking.

Pyruvate

Pyruvate is the end product of glycolysis and represents a mitochondrial fuel entering the TCA cycle after conversion to ACoA. Pyruvate is neuroprotective in models for epilepsy [153] and Alzheimer's disease [83]. The neuroprotective properties of pyruvate are multifaceted and originate from anti-oxidant properties, the ability to facilitate glutamate efflux from the brain, anti-inflammatory effects, and their ability to increase TCA cycling [223]. In the context of ALS, administration of 1 g pyruvate/kg body weight/week to mutant SOD1^{G93A} mice prolonged the lifespan by 12 days, slowed disease progression, and improved motor performance when starting the treatment at the age of 70 days [142]. However, another study in which mutant SOD1^{G93A} mice received 0.5 g/kg body weight six times a week starting from the same age did not improve survival or rotarod performance [59]. There are no clinical trials available assessing the effect of pyruvate intake in ALS patients.

Enhancing mitochondrial function

In the presence of decreased mitochondrial function, providing additional and/or alternative energy substrates may be insufficient. Enhancing mitochondrial function and hence metabolic efficiency may be necessary.

Dichloroacetate

Increasing the conversion of pyruvate into ACoA, by providing the pyruvate dehydrogenase kinase inhibitor dichloroacetate improved survival, delayed disease onset, and reduced spinal motor neuron loss in mutant SOD1^{G93A} mice [131, 141]. As dichloroacetate blunted the reduction of expression of mitochondrial genes seen in mutant SOD1^{G93A} skeletal muscle during disease progression, improving mitochondrial function could elicit this effect [141]. While in NSC34 motor neuron-like cells mutant SOD1 increased pyruvate dehydrogenase kinase expression and lactate production [195], it was not tested if dichloroacetate treatment improved mitochondrial function in the CNS of mutant SOD1^{G93A} mice. Although doses of dichloroacetate used in preclinical ALS studies are well tolerated in patients with advanced solid tumors [33], ALS clinical trials are lacking.

Acetyl-L-carnitine

Acetyl-L-carnitine is the acetyl-ester of L-carnitine. Acetyl-L-carnitine is an important cellular source of acetyl groups to generate ACoA in high-energy demanding situations [139].

Acetyl-L-carnitine also mediates transport of long chain fatty acids across mitochondrial membranes and is, therefore, rate limiting for β -oxidation. While the neuroprotective effects of acetyl-L-carnitine are mainly described in cortical neurons [166, 175], an early study showed neuroprotective and neurotrophic effects of acetyl-L-carnitine in embryonic rat motor neurons [14]. Moreover, administration of L-carnitine to symptomatic mutant SOD1^{G93A} mice improved survival [100]. Based on these findings, a randomized double-blind placebo-controlled phase II trial was performed in 82 patients. Subjects ingested 3 g of acetyl-L-carnitine or placebo each day together with riluzole. Acetyl-L-carnitine was well tolerated, and respiratory capacity and ALSFRS showed mild improvements. In addition, median survival doubled in the acetyl-L-carnitine group compared to the placebo group [11]. Despite these results, a larger phase III trial has not yet been performed.

Conclusion and future perspectives

While dysregulated systemic energy metabolism is now well established in ALS patients, energy metabolism has received a little attention in ALS research due to its association with mutant SOD1 models. It now becomes obvious that abnormal energy metabolism also has a role in more recently developed ALS models [118, 170, 183, 205]. In ALS motor neurons and glia, both mitochondrial and glycolytic energy metabolism seem to be impaired, but the molecular mechanisms underlying energetic stress remain unknown. Since motor neuron physiology is highly energy demanding, impairments in energy metabolism could, at least in part, explain the selective dying of motor neurons in ALS. As a consequence, targeting defects in energy metabolism in ALS represents a rational therapeutic strategy. Manipulating energy metabolism is a particularly potent strategy to treat complex diseases due to its intimate link to epigenetic control [60, 94, 119] and is, therefore, increasingly recognized as therapeutic target in cancer [28], immunodeficiency [123], and stroke [156]. To date, a unifying view on how different metabolic pathways converge and whether metabolic alterations contribute to disease etiology in ALS is non-existing. Future work using direct measurements of metabolic fluxes is clearly needed to obtain a more in-depth understanding of motor neuron metabolism in health and disease. Moreover, due to the compartmentalization of specific energy requiring processes in motor neurons, defining the role of metabolism and ALS-related motor neuron dysfunction requires high-resolution and spatial subdivision of metabolic and functional analyses. Knowing how ALS motor neurons differ metabolically from healthy motor neurons could offer the necessary insights to develop future therapeutic

approaches in ALS. Another relevant area for future research is to explore the metabolic crosstalk between motor neurons and glial cells, as well as other disease-relevant cells such as the muscle.

In conclusion, it is too early to consider ALS at present as a metabolic disease. However, the massive amount of circumstantial evidence linking energy metabolism with ALS pathophysiology underscores the therapeutic potential of targeting metabolism. As is the case for many other pathways and mechanisms proposed to play a crucial role in ALS, the ultimate proof that disturbances in metabolism are causally linked to the selective motor neuron death in ALS will be a positive clinical trial with a therapeutic strategy tackling energy metabolism in patients. In the meantime, we strongly believe that a better understanding of the metabolic biology of ALS could lead to the identification of novel therapeutic targets.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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