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The interplay between metabolic homeostasis and neurodegeneration: insights into the neurometabolic nature of amyotrophic lateral sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal, neurodegenerative disease that is characterized by the selective degeneration of upper motor neurons and lower spinal motor neurons, resulting in the progressive paralysis of all voluntary muscles. Approximately 10 % of ALS cases are linked to known genetic mutations, with the remaining 90 % of cases being sporadic. While the primary pathology in ALS is the selective death of upper and lower motor neurons, numerous studies indicate that an imbalance in whole body and/or cellular metabolism influences the rate of progression of disease. This review summarizes current research surrounding the impact of impaired metabolic physiology in ALS. We extend ideas to consider prospects that lie ahead in terms of how metabolic alterations may impact the selective degeneration of neurons in ALS and how targeting of adenosine triphosphate-sensitive potassium (K_{ATP}) channels may represent a promising approach for obtaining neuroprotection in ALS.

Keywords: Amyotrophic lateral sclerosis, Metabolism, Neurometabolism, Hyperexcitability, Ion channels, K_{ATP} channels

Introduction

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease, initially described in 1869 by Jean-Martin Charcot [1]. ALS is a fatal, neurodegenerative disease in which the primary hallmark is the selective degeneration of upper motor neurons and lower spinal motor neurons. The loss of these motor neurons results in progressive paralysis of all voluntary muscles [2]. The underlying cause for ALS remains unknown, although many hypotheses to explain the selective death of upper and lower motor neurons have been proposed. Causative theories include abnormal protein function and RNA processing [3–7], mitochondrial dysfunction [8], non-cell autonomous death [9, 10], hyperexcitability [11, 12], excitotoxicity [13], and metabolic dysfunction [14]. Despite these theories, it is unlikely that ALS is caused by or results from any single one of these processes.

Approximately 10 % of ALS is defined as being familial, and the remaining 90 % of cases are considered sporadic, [15, 16]. Mutations in a number of genes including *C9orf72* [4, 7], *SOD1* [17], *TARDBP* [5, 18], and *FUS* [19, 20] cause familial ALS and contribute to sporadic ALS (reviewed in [15]). Interestingly, in line with the multifactorial nature of ALS, a recent modelling study by Al-Chalabi and colleagues suggests that in ALS, an underlying genetic susceptibility occurs in combination with environmental factors, which culminates in up to six exposures with the final exposure triggering the onset of disease [21]. Potential environmental risk factors that have been proposed to contribute to ALS include elite athleticism [22–24], β-methylamino-L-alanine (BMAA) [25, 26], pesticides [27, 28], and lifestyle factors (including smoking [29, 30], diet [31–35], and body mass index [36–41]) amongst many others (reviewed in [42]).

Evidence of metabolic dysfunction in ALS was reported throughout the 1970s and 1980s [43, 44]. Since that time, investigation into the contribution of the

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dysregulation in metabolic homeostasis to the pathogenesis of ALS has increased significantly. Numerous studies now indicate that ALS patients have impairments in whole body physiology and energy homeostasis, with data suggesting that an imbalance in energy metabolism appears to negatively influence the rate of progression of disease [14, 36–38, 40, 41, 45–62]. Should this be the case, attempts to offset energy deficits (e.g. through careful nutritional management [63]) to improve prognosis must take the metabolic state and underlying cause of metabolic perturbations of the person living with ALS into consideration. This review will focus on current research investigating the impact of impaired metabolic physiology in ALS and will consider prospects that lie ahead in terms of how metabolic alterations may impact the selective death of neurons in ALS.

Metabolic homeostasis: the complex nature of balancing energy intake with energy expenditure

Metabolic homoeostasis and body composition requires balancing energy intake with energy expenditure. Seemingly simple in theory, the practical underpinnings of maintaining metabolic balance extend well beyond nutrient intake and absorption and resting metabolism and physical activity. Many fundamental regulators of metabolic physiology reside within the endocrine and neuroendocrine systems of the body. For example, orexigenic and anorexigenic neurons in the hypothalamus secrete neuropeptides that stimulate and inhibit appetite, respectively (reviewed in [64]), hormones secreted from the stomach and adipose control appetite (reviewed in [65]), pituitary-derived (e.g. growth hormone) and pancreatic hormones (e.g. insulin) play vital roles in modulating insulin action, glucose metabolism, free fatty acid flux, and body composition (reviewed in [66]), and the interplay between the neuroendocrine and endocrine systems can greatly influence physiological responses during periods of both positive and negative energy balance (reviewed in [67]). Not surprisingly, perturbation to endocrine and neuroendocrine processes typically results in the development of metabolic complications as is seen in type 2 diabetes and metabolic syndrome.

Dysregulation of metabolic homeostasis in ALS: causes and consequences

In ALS patients, growth hormone deficiency [68], glucose intolerance [61], insulin resistance [43], hyperlipidemia [69], hypometabolism [46, 70–72], hypermetabolism [47, 48, 54, 72], and reduced body mass index (BMI) throughout the course of disease [36, 37, 41, 57, 59] are telling signs of the existence and progressive worsening of dysregulated metabolic homeostasis. These observations have sparked attempts to identify the underlying cause and the consequences of metabolic perturbations in ALS.

ALS-causing genes and metabolism

The underlying cause of defective metabolic homeostasis in ALS remains to be fully determined. Mutations in or altered expression of ALS-associated genes in mice, cell lines, and humans are often coupled with metabolic abnormalities. In mice expressing $SOD1^{G86R}$ or $SOD1^{G93A}$ mutations, hypermetabolism and defects in glucose metabolism are observed [14, 60]. Deletion of *TARDP* (TDP-43) in adult mice results in weight loss, depletion of fat mass, and rapid death [73]. By contrast, overexpression of TDP-43 in mice ($TDP\text{-}43^{A315T}$) results in increased fat deposition and hypertrophy of adipocytes [74]. When overexpressed in mouse skeletal muscle, TDP-43 drives an increase in the steady state expression of Tbc1d1, a Rab-GTPase-activating protein. Increased Tbc1d1 expression is thought to reduce insulin-stimulated translocation of the Glut4 transporter from tubulovesicular structures adjacent to the Golgi complex and from vesicles throughout the cytoplasm to the cell surface, impairing insulin-mediated glucose uptake [74]. Moreover, overexpression of human TDP-43 in mice underpins morphological abnormalities during mitochondrial formation [75, 76]. When considering *FUS* mutations, mass spectrometry analysis of protein interactions in HEK293 cells overexpressing mutant *FUS* associated with juvenile ALS demonstrate greater interactions with mitochondrial enzymes and proteins involved in glucose metabolism [77]. Not surprisingly, exogenous expression of mutant *FUS* in HEK293 and SH-SY5Y cells leads to a significant reduction in cellular adenosine triphosphate (ATP) production [77]. Finally, humans with ALS who harbour the *C9orf72* repeat expansion exhibit hypometabolism in numerous brain regions when compared to sporadic ALS patients [70]. Collectively, results indicate that the expression of ALS-associated genes *SOD1*, *TARDP*, *FUS*, and *C9orf72* is tightly linked to processes that are involved in regulating lipid and glucose homeostasis, mitochondrial formation, and ATP production. The presentation of metabolic defects in parallel with ALS-causing gene mutations point to the possible existence of a genetic predisposition to metabolic abnormalities in ALS and suggest a potential integral role for metabolic factors in regulating the progression and development of ALS.

Targets of dysregulated metabolic homeostasis in ALS: the endocrine organs

Pristine physiological responses that occur throughout the body in response to metabolic pressures serve to ensure optimal metabolic flux. In turn, this sustains favourable responses to the metabolic demands of disease, thereby enhancing the likelihood for survival. Interestingly, altered

metabolic homeostasis in ALS presents at the whole body level, and some of the targets that are affected in ALS are major endocrine organs that play crucial roles in regulating glucose and free fatty acid flux. We will briefly consider the adipose tissue, liver and muscle as critical metabolic organs that modulate homeostatic responses during the progression of ALS.

Adipose

Adipose triglycerides represent the largest energy reserve in the human body. Within all cell types, triacylglycerols are stored as cytoplasmic lipid droplets or fat droplets that are enclosed by a monolayer of phospholipids and hydrophobic proteins. Fatty acids that arise from the breakdown of triacylglycerols play crucial roles in membrane biosynthesis, signal transduction, and energy production. Importantly, fatty acids that are derived from adipocyte triacylglycerols and released into circulation are in general, the primary regulators of fatty acid metabolism. Thus, in normal physiology, the maintenance of metabolic homeostasis is critically dependent on the flux between the uptake and storage of lipids (lipogenesis) during periods of positive energy balance and the breakdown and release of lipids (lipolysis) from adipocytes during periods of negative energy balance (reviewed in [78]).

It was first noted in the 1970s that ALS patients have larger subcutaneous fat cells [44], and it has been suggested that defects in carbohydrate metabolism and increased serum triglycerides in ALS patients might be somewhat related to this enlargement of subcutaneous fat cells. More recently, increased expression of a number of fat-derived cytokines (adipokines) that are associated with metabolic disease has been observed in ALS patients [79]. While the significance of these changes remains to be defined, there is evidence to show that the regulation of lipolytic processes to maintain metabolic flux could be key to promoting a survival advantage in ALS. In 2008, Dupuis et al. presented evidence to show that increased low-density lipoprotein:high-density lipoprotein ratio was associated with extended survival in ALS [69]. Subsequent to this, elevated serum triglycerides [51], higher palmitoleate and blood cell palmitoleate:palmitate ratio [80], and higher BMI (commonly used as a measure of increased body "fatness") have been linked to improved survival in ALS [36, 37, 41, 57–59]. Moreover, Lindauer and colleagues have demonstrated a favourable relationship between subcutaneous adiposity and survival in ALS patients [81]. Thus, current studies suggest that the availability and mobilization of lipids from larger subcutaneous adipose stores into circulation may play a fundamental role in modulating the course of disease. In this regard, a greater capacity to mobilize lipids may favourably impact disease progression. The mechanisms by which increased fat mass or increased movement of lipids into circulation exerts beneficial effects in ALS remain to be determined, but it is plausible that the availability of excess fatty acids may assist in the provision of an alternative metabolic substrate to meet energy demand in ALS.

Liver

The liver is an essential endocrine organ that regulates lipogenesis, gluconeogenesis, and cholesterol metabolism; it is a major site at which carbohydrates, proteins, and lipids are synthesized, metabolized, stored, and redistributed. Under fed states, the liver stores glycogen and triglyceride (which is later redistributed to adipose). In the fasted state, the liver releases glucose (formed via gluconeogenesis) and ketone bodies (produced from fatty acids). Influenced by glucose, insulin, and glucagon, liver carbohydrate and fatty acid metabolism orient metabolic fluxes towards energy storage or substrate release (reviewed in [82]).

Ultrastructural abnormalities in the liver [83–86], fatty acid infiltration into the liver [86], and mild liver dysfunction have been observed in ALS patients [86]. More recently, hepatic steatosis has been reported to be a frequent occurrence in ALS [69, 87]. While the discussions surrounding the prognostic and metabolic implications of hepatic steatosis in ALS remain open, abnormal insulin-like growth factor-1 (IGF-1) axis function alongside lipid redistribution in $SOD1^{G93A}$ mice [88], and dysregulation of lipid metabolism in response to genetic ablation of TDP-43 in mice [73] provide a foundation upon which the beneficial effects of altered hepatic lipid metabolism in ALS can be explored.

Skeletal muscle

Skeletal muscle is a major consumer of glucose and thus plays a fundamental role in the maintenance of glucose homeostasis and carbohydrate metabolism. Skeletal muscle is dependent upon small quantities of blood glucose during periods of rest or fasting. However, after insulin stimulation, the need for blood glucose in the skeletal muscle increases to approximately 75 % of that required by the body [89, 90]. Given its metabolically demanding nature, it has been proposed that metabolic defects in ALS originate from the skeletal muscle [91]. In support of this, muscle-restricted expression of the superoxide dismutase 1 (SOD1) gene causes muscle atrophy via oxidative damage and mitochondrial dysfunction [91, 92], and muscle restricted mitochondrial dysfunction drives motor neuron degeneration [93]. Moreover, in ALS skeletal muscle, structural and functional abnormalities in mitochondria [94–96], impaired glucose use and oxidative mitochondrial metabolism [60, 97–100], defective activity of respiratory complexes I and IV [95, 96, 101], and reduced cellular ATP [97]

exist. More recently, using the $SOD1^{G86R}$ mouse model of ALS, Palamuic and colleagues demonstrate that skeletal muscle mitochondrial dysfunction and denervation in ALS likely occurs due to a decreased ability to generate energy via glucose metabolism [60]. Consistent with this, our analysis of the skeletal muscle from the $SOD1^{G93A}$ mouse model of ALS (B6.Cg-Tg(SOD1-G93A)1Gur/J; all $SOD1^{G93A}$ mice had ≥ 25 copies of the SOD1 gene) using a mouse Glucose Metabolism RT2 Profiler PCR Array (PAMM-006Z, QIAGEN, Germany, strictly adhering to supplied protocols and guidelines) illustrate altered expression of a number of genes critically involved in the processes that regulate muscle glucose metabolism (listed in Table 1), starting at disease onset (8 weeks of age) and continuing through to mid-stage (18 weeks of age) and end-stage (24 weeks of age) of disease (Fig. 1). Compared to non-transgenic littermate control mice, we observed a marked decrease in genes central to all processes that are associated with glucose metabolism (including glycolysis, tricarboxylic acid (TCA) cycle, gluconeogenesis, and glucose regulation) and glycogen metabolism (including glycogen synthesis, regulation, and degradation). We

Table 1 Gene descriptions and identifiers for data described in Fig. 1

Symbol	Description	Gene symbol	UniGene identifier	NCBI RefSeq
Aco1	Aconitase 1	AI256519, Aco-1, Irebp, Irp1	Mm.331547	NM_007386
Aco2	Aconitase 2, mitochondrial	Aco-2, Aco3, D10Wsu183e	Mm.154581	NM_080633
Aldob	Aldolase B, fructose-bisphosphate	Aldo-2, Aldo2, BC016435, MGC36398	Mm.482116	NM_144903
Bpgm	2,3-Bisphosphoglycerate mutase	AI323730, AL022789, C86192	Mm.28263	NM_007563
Dld	Dihydrolipoamide dehydrogenase	AI315664, AI746344	Mm.3131	NM_007861
Eno1	Enolase 1, alpha non-neuron	0610008I15, AL022784, Eno-1, MBP-1, MGC103111, MGC107267	Mm.70666	NM_023119
Eno3	Enolase 3, beta muscle	Eno-3	Mm.251322	NM_007933
Gbe1	Glucan (1,4-alpha-), branching enzyme 1	2310045H19Rik, 2810426P10Rik, D16Ertd536e	Mm.396102	NM_028803
Gys1	Glycogen synthase 1, muscle	Gys3, MGS	Mm.275654	NM_030678
Gys2	Glycogen synthase 2	BC021322, LGS, MGC29379	Mm.275975	NM_145572
Idh1	Isocitrate dehydrogenase 1 (NADP+), soluble	AI31485, AI788952, E030024J03Rik, Id-1, Idh-1, Idpc, MGC115782	Mm.9925	NM_010497
Idh2	Isocitrate dehydrogenase 2 (NADP+), mitochondrial	E430004F23, IDPm, Idh-2	Mm.246432	NM_173011
Mdh1	Malate dehydrogenase 1, NAD (soluble)	B230377B03Rik, D17921, MDH-s, MDHA, Mor-2, Mor2	Mm.212703	NM_008618
Mdh1b	Malate dehydrogenase 1B, NAD (soluble)	1700124B08Rik, AV255588	Mm.30494	NM-029696
Pck1	Phosphoenolpyruvate carboxykinase 1, cytosolic	AI265463. PEPCK, Pck-1	Mm.266867	NM_011044
Pdk4	Pyruvate dehydrogenase kinase, isoenzyme 4	AV005916	Mm.235547	NM_013743
Pgk1	Phosphoglycerate kinase 1	MGC118097, Pgk-1	Mm.336205	NM_008823
Phka1	Phosphorylase kinase alpha 1	5330411D17, 9830108K24Rik, Phka	Mm.212889	NM_173021
Phkb	Phosphorylase kinase beta	AI462371, MGC62514	Mm.237296	NM_199446
Phkg1	Phosphorylase kinase gamma 1	Phkg	Mm.3159	NM_011079
Pygm	Muscle glycogen phosphorylase	AI115133, PG	Mm.27806	NM_011224
Sdha	Succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	1500032O14Rik, 2310034D06Rik, 4921513A11, C81073, FP, SDH2, SDHF	Mm.158231	NM_023281
Sdhb	Succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	0710008N11Rik	Mm.246965	NM_023374
Sdhc	Succinate dehydrogenase complex, subunit C, integral membrane protein	0610010E03Rik, AI316496, AU019277, MGC103103	Mm.198138	NM_025321
Sucla2	Succinate-coenzyme A ligase, ADP-forming, beta subunit	4930547K18Rik	Mm.38951	NM_011506
Suclg2	Succinate-coenzyme A ligase, GDP-forming, beta subunit	AF171077, AW556404, D6Wsu120e, MGC91183	Mm.371585	NM_011507
Tpi1	Triosephosphate isomerase 1	AI255506, Tpi, Tpi-1	Mm.4222	NM_009415
Ugp2	UDP-glucose pyrophosphorylase 2	MGC38262	Mm.28877	NM_139297

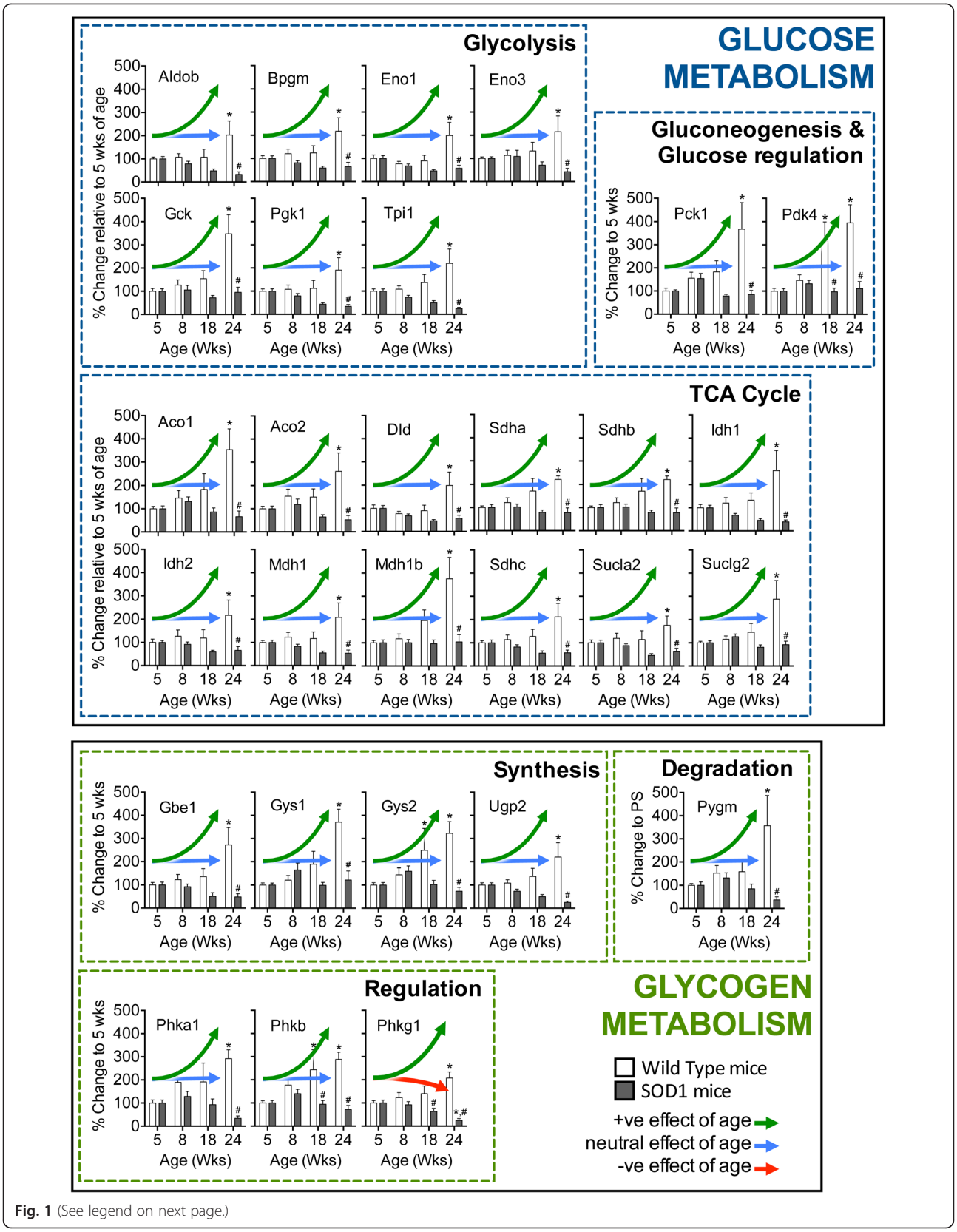

Fig. 1 (See legend on next page.)

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Fig. 1 Expression of glucose and glycogen metabolism genes in the skeletal muscle of wild-type and SOD1^{G93A} mice. Compared to non-transgenic wild-type mice (*white bars*), the expression of glucose and glycogen metabolism genes in the skeletal muscle of SOD1^{G93A} mice (*black bars*) does not increase over the assessed period of muscle growth. Disease stages by age: pre-symptomatic (5 weeks), onset (8 weeks), mid-stage (18 weeks), and end-stage (24 weeks). *Green upward arrows* illustrate a significant effect ($p < 0.05$) of age following analysis by two-way ANOVA. *Blue arrows* represent no effect of age ($p > 0.05$) following analysis by two-way ANOVA. For SOD1^{G93A} mice, relative expression of *Phkg1* mRNA declined with age (illustrated by *red downward arrow*). The effect of age on gene expression was further interrogated using multiple comparison assessment with Bonferroni post hoc analysis; *significant differences ($p < 0.05$) at 8, 18, and 24 weeks of age when compared to 5 weeks of age. An effect of genotype within each age (5, 8, 18, and 24) was interrogated using multiple comparison assessment with Bonferroni post hoc analysis; $^{\#}$significant ($p < 0.05$) differences between WT and SOD1^{G93A} mice at 5, 8, 18, or 24 weeks of age ($n = 6$ mice/group). Data presented as mean ± SEM. Gene descriptions, symbols, UniGene identifiers, and NCBI reference sequences (NCBI RefSeq) are provided in Table 1

observed a significant reduction in mRNA expression for the majority of target genes in the skeletal muscle of SOD1^{G93A} mice when compared to the progressive rise in gene expression that is normally observed in non-transgenic wild-type mice during the first 3 months of age (when muscle growth is occurring [102]). Observations suggest that metabolic processes that underpin the establishment of glucose use by muscle in ALS may be compromised, potentially reflecting the disease pathology. Whether altered expression patterns of glucose and glycogen metabolism genes are due to the overexpression of the human SOD1 gene, which itself is proposed to induce ALS-like pathologies observed in SOD1 mice [103–106], remains to be determined.

When glucose is not used for energy in the skeletal muscle, fatty acids [107] and ketones (which are a by-product of the metabolism of fat) can fuel ongoing energy demand [108]. Thus, it is not surprising that observations from SOD1^{G86R} mice identify increased peripheral clearance of lipids in response to supplementation with a high-fat diet [53]. Whether these measures of peripheral lipid clearance reflect an underlying physiological response to replace atrophic muscle with fat, fat accumulation due to denervation of muscle fibres, or fat/ketone transport into muscle for use as an alternative energy substrate remains unknown. Recent observations demonstrating an increase in the expression of genes that are critical in regulating fat metabolism in the skeletal muscle prior to denervation and improved endurance exercise performance in SOD1^{G86R} mice are congruent with the notion that there is a switch in energy substrate preference in the skeletal muscle from glucose towards fat [60]. While these data are convincing in proposing that reduced glucose metabolism in the skeletal muscle contributes to ALS pathophysiology (and reported fatigue [109]), muscle weakness in ALS is ultimately due to the loss of innervation from the dying neuron.

Central hypermetabolism and hypometabolism: implications for neuronal death

A number of in vivo and in vitro studies have investigated brain or neuronal metabolism to provide insight into how the metabolic profile of neural cells might be associated with ALS neuropathology. Brain hypermetabolism has been observed in bilateral amygdalae, midbrain, pons, cerebellum, bilateral occipital cortex, globus pallidus, left inferior temporal cortex, temporal pole, and the hippocampus [45, 70, 72]. Given that this hypermetabolism has been attributed to the local activation of glial cells, it is likely that neurons in these brain regions are subjected to an environment that promotes non-cell autonomous death through the expression of mutant SOD1 [9, 10] or an α2-Na/K ATPase/α-adducin complex [110] in astrocytes. Brain hypometabolism (decreased use of glucose) is observed in frontal, motor, and occipital cortices, right insula, anterior and posterior cingulate, precuneus, inferior parietal lobe, caudate, thalamus, putamen, and the left frontal and superior temporal cortex of ALS patients [45, 70–72, 111, 112]. In addition, reduced glucose use has also been reported to occur in the spinal cords of SOD1^{G93A} mice [113]. Thus, it is plausible that decreased glucose metabolism leads to an increased dependence on alternate energy substrates (e.g. ketones that arise from the oxidation of fat that is mobilized from storage [53]) to fuel survival. It is also feasible that defects in the capacity for neurons to use glucose as an energy substrate may lead to metabolic deficits that underpin the death of neurons in ALS. Indeed, decreased production of energy in the form of ATP and decreased glycolytic capacity in response to oxidative stress in NSC-34 motoneuron-like cells harbouring the SOD1^{G93A} mutation [114] indicate that impaired neuronal bioenergetics may play a role in the death of neurons in ALS.

The metabolic demands of the neuron and the consequences of neuronal ATP depletion

The central nervous system comprises a complex network of highly organized and distinct neural circuits that mediate interneuronal communication. Energy demand in the brain is high. While accounting for approximately 2 % of total body mass, the human brain consumes 20 % of the total oxygen used by the body. Of the neural cell subtypes in the brain, energy consumption is predominantly demanded by the neurons, with astrocytes contributing only 5–15 % of the brain energy requirement [115].

Neurons are particularly active cells and, thus, have high metabolic demand. The metabolic processes in the neuron consists of (1) submembrane glycolysis, which is linked to the pumping of ions across the cell membrane, (2) aerobic glycolysis, which allows for the generation of pyruvate to fuel aerobic metabolism, and (3) the production of NADH/ATP in the mitochondria by means of the TCA cycle [116]. Although a low level of basal metabolism is critical for maintaining the survival of the cell, for active neurons, an increase in the metabolic demand that is required for the generation of action potentials [117] and their large surface area amounts to a considerable metabolic load that must be met through the generation of ATP. Neurons are extremely dependent on aerobic metabolism and oxygen use, but despite a large reservoir of ATP, reduced glycolytic and/or mitochondrial function modifies ATP availability, and glucose and oxygen deprivation in neurons results in cell death [118, 119]. Thus, when neurons are more active, increased local blood flow and increased substrate delivery from neighbouring cells is of critical importance to meet metabolic requirements and sustain cellular survival. As such, upon activation, neurons indirectly regulate their own metabolism by releasing by-products (e.g. nitric oxide and glutamate) that influence the surrounding cells and blood vessels [120–123]. This leads to the activation of astrocytes and increased levels of oxygen, lactate and glucose [117, 124, 125]. Despite categorical evidence that glucose is the chief energy substrate that is used by the brain to sustain metabolic demand, there is evidence to suggest that lactate can also be taken up by neurons to fuel aerobic metabolism [116, 124, 125]; it is postulated that the neuron-astrocyte lactate shuttle is the structure that permits the transfer of lactate from astrocytes to neurons for use as an additional metabolic substrate to fuel synaptic transmission [126–130]. With lactate being proposed to be a critical source of energy for active neurons, the lactate shuttle hypothesis postulates that neuronal-glutamate released during synaptic transmission drives aerobic glycolysis in astrocytes. Following this, glutamate is re-sequestered into astrocytes, resulting in the activation of the Na+/K+-ATPase, which in turn drives the use of cellular ATP. This initiates the uptake and processing of glucose and, finally, the release of lactate from astrocytes [127–129]. In line with a role for the lactate shuttle in the maintenance of neuronal energy demand, neurons express lactate dehydrogenase isoforms that favour the conversion of lactate to pyruvate and monocarboxylate transport (MCT2) receptors that take up pyruvate and lactate at high affinity. Thus, neurons in general, appear appropriately equipped to accommodate for their high metabolic demand [121, 131–134].

In ALS however, a combination of defective energy metabolism [14, 46], decreased glucose use in the cortex and spinal cord [49, 71, 135, 136], reduced expression of TCA cycle intermediates in the brain and spinal cord [137], damaged neuronal mitochondria [138–140], and mitochondrial electron transport chain dysfunction [8, 141, 142] suggest that a bioenergetic limitation exists throughout the course of disease and that the generation of neuronal ATP is compromised. Moreover, reduced lactate transport to neurons [119] and impaired lactate metabolism and impaired trafficking of lactate between neurons and astrocytes in SOD1-related ALS [143] suggest that defects in the lactate shuttle might further contribute to bioenergetic deficit in neuronal cells in ALS. Consequently, defects in neuronal metabolism may exist regardless of the provision of alternative energy substrates (e.g. through high calorie feeding [14, 50, 53, 62, 144] or ketogenic diet [145]) to sustain or improve neuronal energy supply. In this regard, treatments that serve to promote or recover the capacity to sustain cellular energy production will be fundamental to prevent neuronal death since deficits in the production of ATP in the presence of escalating metabolic pressures may underlie the selective and unrelenting death of neurons while exacerbating disease progression during later stages of ALS. Indeed, the consequences of ATP deficit has recently been highlighted in a modelling study that links cellular activity and vulnerability to degeneration to inadequate levels of cellular energy [146]. In this model, a deficit in ATP underpins higher metabolic cost to the neuron. This exacerbates energy deficit and disrupts cellular ionic gradients, triggering chronic and irreversible depolarisation (hyperexcitability) and neuronal death via ATP depletion [146].

Neuronal hyperexcitability is observed in ALS [11] and can be defined as an exaggerated response to a stimulus, which under normal circumstances would elicit an otherwise standard response. A positive correlation has been observed between increased axonal hyperexcitability [147–149] and disease progression in ALS patients [148], suggesting that alterations in the membrane excitability of axons that are distal to the neuron cell body might be central to the disease process. Critically, however, neuronal hyperexcitability, which may underpin the degeneration of neurons and their associated connections in ALS, has been found to occur early in the course of human ALS [11, 150] and in motor cortex layer V pyramidal neurons of $SOD1^{G93A}$ mice [151].

The excitability of a neuron and the generation of action potentials within neurons are dependent upon calcium (Ca^{2+}), sodium (Na^{+}), and potassium (K^{+}) channels. Importantly, the opening of voltage-gated K^{+} channels evokes the repolarisation of the cell to the resting potential. This allows the neuron to reduce calcium influx and

thus decrease synaptic release of glutamate [152]. In light of a mathematical model proposing that axonal hyperexcitability in ALS might be due to impaired voltage-gated K^+ currents [148], it has recently been shown that a similar impairment in voltage-gated K^+ currents exists at the level of the neuron. Retigabine-induced activation of voltage-gated M-type K^+ channels in SOD1 motor neurons derived from ALS patient-induced pluripotent stem cells (iPSCs) resulted in the reversal of intrinsic membrane hyperexcitability [12]. With evidence demonstrating that retigabine is also able to extend the survival of iPSC-derived SOD1 motor neurons from ALS patients, it is plausible that the activation of other K^+ ion channels that function to attenuate neuronal depolarisation might produce protective effects in ALS. From an energetic perspective, increased Na^+ influx associated with hyperexcitability in ALS may lead to overloading of the neuronal Na^+-K^+ ATPase-dependent pump resulting in excessive use of cellular ATP, energy failure, and neuronal death. Thus, other potential target candidates for attenuating chronic neuronal depolarisation in ALS may include K^+ channels which couple the metabolic state of the cell to its activity.

ATP-sensitive potassium (K_{ATP}) channels: a new target in ALS?

K_{ATP} channels are octameric protein complexes that are made up of four pore-forming Kir6 inwardly rectifying potassium channel family (Kir) subunits and four regulatory sulfonylurea receptor (SUR) subunits [153, 154]. K_{ATP} channels play fundamental roles in cellular physiology. By regulating the flux of K^+ across the cell membrane, K_{ATP} channels link the metabolic state of the cell to its electrical activity [155]. An increase in energy metabolism (and high ATP levels) drives the closure of K_{ATP} channels, resulting in membrane depolarization and electrical activity. By contrast, in response to metabolic deficit (and low ATP levels), K_{ATP} channels open, thereby driving a suppression in electrical activity [156]. Essentially glucosensing, K_{ATP} channels are regulated by the bioenergetic state of the cell (i.e. intracellular levels of ATP) [156]. Interestingly, K_{ATP} channels are also lactate sensing [157–160], and it has been postulated that they may modulate neuronal excitability in response to an increase in cytosolic ATP that is generated from the oxidation of astrocyte-derived lactate [161].

With mounting evidence to suggest that decreased cellular ATP production and subsequent alterations in cellular membrane excitability is associated with neurodegenerative disease and neuronal death [146, 162], it has been proposed that pharmacological mediators of K_{ATP} channels may prove to be promising targets for alleviating the neurodegenerative processes associated with disease or with neurotoxic insults [162–164]. However, while K_{ATP} channels are widely expressed [165–169], the biophysical, pharmacological, and metabolic properties of functional K_{ATP} channels are dictated by subunit composition [170, 171]. For example, channels that are formed by Kir6.2 and SUR1 are highly sensitive to diazoxide and are inhibited by ATP, and they express biophysical properties that are seen in pancreatic β cells [172, 173]. Conversely, Kir6.2/SUR2A K_{ATP} channels are somewhat insensitive to diazoxide, and they are predominantly expressed in the cardiac and skeletal muscle [171, 174]. Kir6.1/SUR2B or Kir6.2/SUR2B K_{ATP} channels possess properties reminiscent of those studied in the smooth muscle. While functional mitochondrial K_{ATP} channels have been proposed to be composed of various subunits [175–177], it is generally accepted that the molecular identity of such channels is yet to be determined. Of interest to neurodegeneration and ALS, Kir6.2/SUR1 K_{ATP} channels are widely expressed on neurons in the brain [168, 169, 178], and pharmacological targeting of such channels has proven to be promising in conditions that are associated with neuronal death.

Diazoxide is a well-known small molecule that activates K_{ATP} channels, including Kir6.2/SUR1 K_{ATP} channels [179]. The neuroprotective effects of diazoxide have been demonstrated in numerous studies. In cerebral ischemia-reperfusion injury, diazoxide reduces levels of reactive oxygen species, decreases DNA oxidative damage, inhibits apoptosis [180–182], and reduces infarct size during ischemia [183]. In the context of Parkinson's disease, diazoxide reduces akinesia [184], protects dopaminergic neurons from death by reducing astrocyte and microglial activation [185], and reduces neuroinflammation associated with activated microglia [186]. In in vitro and in vivo models of Alzheimer's disease, activation of K_{ATP} channels by diazoxide protects against β-amyloid toxicity, reducing protein aggregation and tau hyperphosphorylation [163, 187]. Finally, in addition to having been shown to reduce glutamate excitotoxicity in epilepsy [188], diazoxide also protects NSC-34 motoneurons from glutamate-mediated cell death, hydrogen peroxide-mediated cell death, and inflammatory damage associated with microglial activation, while decreasing neuronal death in hippocampal slices after N-methyl-D-aspartic acid (NMDA)-induced excitotoxicity [189].

The use of diazoxide and the investigation of its neuroprotective potential and role in ALS however is relatively less well studied. Interestingly, however, a patent describing oral administration of low doses of diazoxide in $SOD1^{G93A}$ mice reported improved median values for survival when compared to non-diazoxide-supplemented $SOD1^{G93A}$ mice [190]. Whether this improved survival outcome in diazoxide-supplemented mice is due to the ability for diazoxide to (a) improve insulin sensitivity and glucose metabolism (thereby presumably counteracting

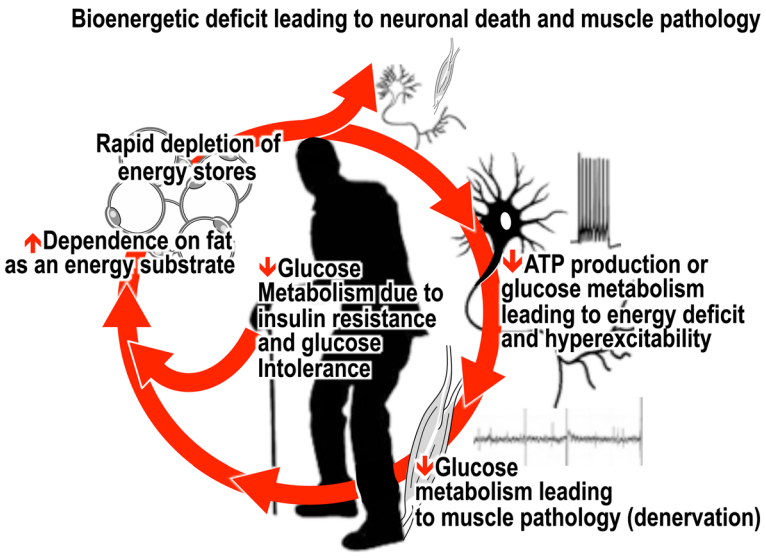

Fig. 2 Decreased production of adenosine triphosphate or decreased glucose metabolism in neurons and decreased glucose metabolism in the skeletal muscle may contribute to the hyperexcitability and selective degeneration of upper and lower motor neurons and muscle pathology/denervation in ALS, respectively. Insulin resistance and glucose intolerance may underpin an inability to efficiently use glucose as an energy substrate. Overall, an inabillity to use glucose in the periphery, in neurons and in skeletal muscle will result in an increased dependence on the use of fat as an energy substrate to offset energy deficit. With escalating metabolic pressure, the rapid depletion of endogenous energy stores will result in a catastrophic failure to meet increased metabolic demand. Thus, a vicious cycle of bioenergetic deficit may underpin or exacerbate disease pathogenesis in ALS

systemic defects in metabolic homeostasis [191]), (b) cross the blood-brain barrier [192] to counteract intrinsic cellular excitability (as has been shown in immature entorhinal cortex neurons [193]), or (c) counteract chronic depolarization that might arise from persistent ATP deficit [146] in response to decreased glucose use [49, 71, 135, 136] and defective function of the astrocyte-lactate shuttle in ALS [143] remains to be determined. Regardless, there is substantial evidence to suggest that the pharmacological modulation of metabolically sensitive K_{ATP} channels by diazoxide (or other specific activators) represents a promising approach for obtaining neuroprotection in neurodegenerative diseases, including ALS.

Conclusions and considerations

The debilitating nature of ALS and the lack of effective treatments against this insidious disease highlight the need to identify therapeutic targets that are amenable to therapy. While systemic manifestation of energy deficit presenting as hypermetabolism, malnutrition, and decreased fat stores (due to increased dependence on fat as an energy substrate) is clearly associated with disease course, what is more striking is the notion that bioenergetic deficit (due to decreased ATP production or decreased glucose metabolism) may contribute in part to the hyperexcitability and selective degeneration of upper and lower motor neurons and muscle pathology/denervation in ALS. When considering all metabolic components, it may well be that a vicious cycle of bioenergetic deficit underpins or exacerbates disease pathogenesis in ALS (Fig. 2). Whether the activation or deactivation of metabolically sensitive K_{ATP} channels and their regulation of systemic metabolic homeostasis and cellular excitability ultimately contribute to neuronal hyperexcitability and the subsequent degeneration of neural networks that are linked to hyperexcitable cells in ALS remains unknown. Nonetheless, the potential for K_{ATP} channels to be novel targets for the treatment of ALS is of significance, as the current availability of a number of compounds that are selective for K_{ATP} channels will greatly facilitate the pharmacological modulation of K_{ATP} channels as an avenue for future scientific investigation in ALS. The knowledge that promises to be gained from such studies will determine whether targeting of metabolic pathways or accommodation for metabolic dysfunction presents as promising therapeutic targets in ALS.

Abbreviations

ALS: amyotrophic lateral sclerosis; ATP: adenosine triphosphate; BMI: body mass index; Ca^{2+}: calcium; IGF-1: insulin-like growth factor 1; iPSCs: induced pluripotent stem cells; K^+: potassium; Kir: inwardly rectifying potassium channels; MCT2: monocarboxylate transporter 2; Na^+: sodium; NADH: nicotinamide adenine dinucleotide (reduced); NMDA: N-methyl-D-aspartic acid; SOD1: superoxide dismutase 1; SUR: sulfonylurea; TCA: tricarboxylic acid.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions
STN conducted the literature review, collated information, and wrote the manuscript. STN interpreted data from the gene array analysis. FJS conducted gene array analysis and interpreted the data. FJS wrote the manuscript. All authors read and approved the final manuscript.

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