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Glucose metabolism in amyotrophic lateral sclerosis: it is bitter-sweet

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A recent study by McDonald et al. (2021) focused on how peripheral glucose metabolism and handling are compromised in amyotrophic lateral sclerosis (ALS). Dysfunctions in glucose and energy metabolism have been identified in transgenic mouse models and patients with ALS. However, how these processes are altered and contribute to disease progression are not fully understood. The aforementioned study has identified several changes to glucose homeostasis in the transgenic SOD1^{G93A} mouse model of ALS at the later stages of the disease. Specifically, the authors found that despite insulin resistance being present, there was increased glucose uptake in ALS mice, and increased glycogen accumulation in the liver. Additionally, there was evidence of glucagon resistance developing in these mice, which supports clinical observations. This perspective outlines the key aspects of glucose metabolism and demonstrates how multiple pathways relating to these processes are compromised in ALS.

Amyotrophic lateral sclerosis: ALS is a progressive neurodegenerative disorder that is characterized by the selective degeneration of upper and lower motor neurons. The death of motor neurons results in the weakness and atrophy of the muscles in the limbs and bulbar region. The progressive weakness and deterioration in motor function ultimately cause paralysis in patients with death commonly due to respiratory failure. There are currently no effective treatments that can cure or halt the progression of the disease. The specific mechanisms underlying motor neuron death during disease progression are still unknown. The general consensus is that ALS consists of multiple pathogenic processes, such as the aggregation of misfolded proteins within cells, glutamate excitotoxicity, neuroinflammation, oxidative stress, and defective energy metabolism. There is growing evidence indicating that abnormal whole-body metabolism could play an important role in driving the progression of ALS, with evidence from both animal models and patients showing increased resting energy expenditure and a decline in body mass index linked to worsened prognosis (Steyn et al., 2018).

Glucose metabolism: Under normal physiological conditions, glucose metabolism begins following the uptake of extracellular glucose by the glucose transporter (GLUT) family, which is subsequently followed by a series of enzymatic reactions to generate energy in the form of adenosine triphosphate (ATP). The overall pathway of glucose metabolism is tightly regulated by both enzymes and hormones and indeed, perturbations at various steps in glucose metabolism have been described in different ALS models (**Figure 1A**). A reduction in glucose uptake has been identified in spinal cords and several brain regions, including motor, frontal and occipital cortex of both human and animal models of ALS, which coexist with reduced glucose consumption and functional changes in the associated regions (Tefera et al., 2021). Interestingly, glucose uptake in the peripheral tissues involved in glucose disposal, specifically skeletal muscles, adipose tissue, and liver was also observed to be increased in the SOD1^{G93A} mice at mid-symptomatic stage of disease through a mechanism independent of insulin levels (McDonald et al., 2021). It is plausible that changes in metabolic homeostasis might underlie the upregulation of glucose uptake in an attempt to maintain glucose availability. At early pre-symptomatic stage, studies have demonstrated a selective loss of glycolytic fibers with a metabolic transition towards an oxidative metabolism in skeletal muscles of ALS. Glycolytic skeletal muscle of SOD1^{G93A} mice showed a marked reduction in activity of phosphofructokinase, a key enzyme involves in glucose metabolism, in concomitant with increase in mitochondrial mass and expression of oxidative/intermediate myosin heavy chain (MHC) IIa isoform, as well as preservation of pure oxidative MHC I isoform at onset stage of disease (Palamiuc et al., 2015; Scaricamazza et al., 2020). This transition is likely an adaptive response to support the functional requirements by recruiting the surviving motor units in the face of defective glycolytic activity. However, despite this, the rate of ATP production, mitochondrial function and complex activities were still significantly compromised in glycolytic muscles of SOD1^{G93A} mice, demonstrating that glucose metabolism is downregulated at the early phase of disease. Interestingly, these findings of mitochondrial defects were only detectable in the spinal cord at symptomatic stage of disease, suggesting that metabolic alterations in skeletal muscle occur independently of neuropathology and may underlie early pathological events in ALS given its role in energy homeostasis (Scaricamazza et al., 2020). Alternatively, to compensate for mitochondrial dysfunction and defective glucose utilization, transition from glucose to lipid metabolism is evident by increased dependence and capacity of lipid mobilization demonstrated in the early phase of disease in SOD1^{G93A} mice. This metabolic shift is further exacerbated by the severe impairments in glucose oxidation as the disease progresses (Palamiuc et al., 2015; Scaricamazza et al., 2020). In addition, induced pluripotent stem cell-derived motor neurons from C9orf72-linked ALS patients and C9orf72 knockout mouse embryonic fibroblasts showed evidence of enhanced lipogenesis and lipophagy, further highlighting dysregulated lipid metabolism in ALS (Liu et al., 2018). Although utilization of fatty acids may pose an initial bioenergetic benefit, persistent fatty acid oxidation can be detrimental to mitochondrial function due to increased reactive oxygen species generated and thus potentially exacerbating degenerative processes. Taken together, whether these metabolic changes in ALS are compensatory or causative effects remain elusive and longitudinal study could potentially provide pathophysiological insights to different metabolic changes in various ALS tissues. Nevertheless, improving metabolic capacity by targeting glycolysis, providing alternative energy substrates to glucose and restoring mitochondrial biogenesis could be promising therapeutic targets for ALS.

Hormonal regulation of glucose homeostasis: Glucose metabolism is tightly regulated through the opposing effects of two hormones released from the pancreas: insulin and glucagon. In response to high blood glucose concentrations, insulin is released from pancreatic β-cells and binds to its receptors in the liver, skeletal muscle, and adipose tissue to reduce blood glucose levels. In the liver, insulin works by promoting the production of glycogen and fatty acids. In adipose tissue and skeletal muscle, insulin promotes the uptake of glucose from the blood by translocating GLUT4, an insulin-dependent transporter to the cell membrane. Indeed,

both protein levels and translocation of GLUT4 were significantly downregulated in response to insulin in skeletal muscles of MLC/SOD1^{G93A} and TDP-43 (A315T) transgenic mouse model of ALS, resulting in reduced blood glucose clearance capacity (Stallings et al., 2013; Dobrowolny et al., 2018). It would be expected that muscle atrophy would contribute to the insulin resistance that is observed in ALS; however, studies have found that this alone is unlikely to contribute to aberrant glucose handling (Pradat et al., 2010). In spite of this, insulin-independent mechanisms of glucose uptake have been identified, possibly to compensate for the insensitivity of tissues to insulin. The study performed by McDonald et al. (2021) has confirmed evidence for this, and has also identified changes to β-cells in the pancreas with disease progression. At the onset of symptoms, pancreatic β-cells remained intact and insulin secretion was unchanged, however, as disease progressed β-cell mass decreased. It is possible that the loss of β-cells in the pancreas at the later stage of disease could be due to overstimulation. Specifically, high blood glucose levels lead to the β-cells secreting insulin but as the ALS target tissues are unresponsive, this causes the blood glucose levels to remain unchanged, hence leading to more β-cell stimulation (**Figure 1B**). Eventually, this can cause detrimental damage to β-cells and their function, leaving the regulation of blood glucose levels to other insulin-independent mechanisms – some of which may include other GLUT isoforms present in the body. In support of this notion, overexpression of GLUT3 in the motor neurons of TDP-43 (WT) or TDP-43 (G298S) expressing drosophila has been shown to alleviate features of TDP-43 proteinopathy, possibly by increasing glucose availability and restoring metabolic homeostasis (Manzo et al., 2019). However, whether such protective effect occurs in the systemic will require further study. There are currently no published studies examining how β-cells are lost in the context of ALS, which is another possible avenue to explore in future studies.

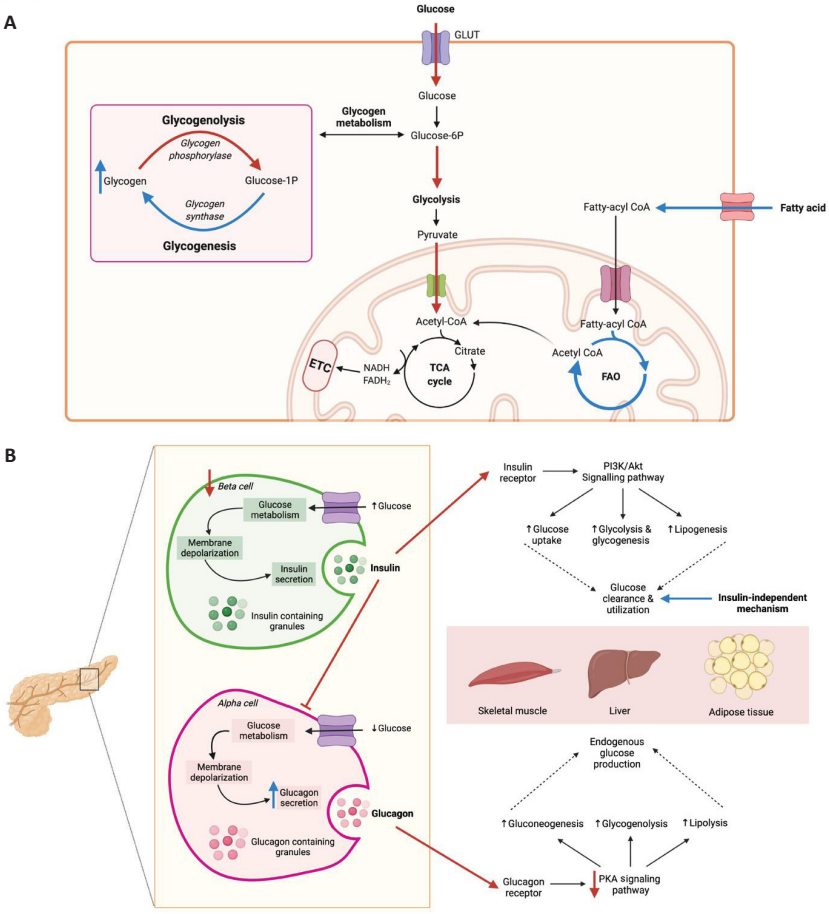

Figure 1 | **Proposed mechanisms for alterations in glucose metabolism and homeostasis in ALS.** Upregulated processes in the pathway are indicated in blue and downregulated processes are indicated in red. (A) Glucose utilization is reduced in ALS by the changes in activities of glucose transporter and glycolytic enzymes, which ultimately results in reduced intermediate metabolites entering TCA cycle and ETC for ATP production. Changes in enzymatic activity involved in the degradative pathway of glycogen (glycogenolysis) and increased production of glycogen (glycogenesis) contribute to the overaccumulation of glycogen in ALS. Deficits in glucose utilization also drive the cell to preferentially use FAO by increasing activities of fatty acid transporter and lipogenic enzymes. Adapted from "Warburg Effect", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates. (B) Systemic impairments of glucose homeostasis in ALS are caused by changes in the actions of both insulin and glucagon. Reduction in insulin levels and sensitivity induced by the loss of beta cell mass could potentially promote glucose clearance through an insulin-independent mechanism of action. In addition to glucagon resistance and impairment in the glucagon signaling pathway, decreased levels of insulin could also downregulate paracrine inhibitory effects on glucagon secretion from the alpha cell, leading to increased circulating glucagon levels. Created with BioRender.com. Acetyl-CoA: Acetyl coenzyme A; ALS: amyotrophic lateral sclerosis; ATP: adenosine triphosphate; ETC: electron transport chain; FADH2: 1,5-dihydroflavin adenine dinucleotide; FAO: fatty acid oxidation; Fatty-acyl CoA: fatty-acyl coenzyme A; Glucose-1P: glucose-1-phosphate; Glucose-6P: glucose-6-phosphate; GLUT: glucose transporter; NADH: 1,4-dihydronicotinamide adenine dinucleotide; PI3K/Akt: phosphatidylinositol 3-kinase/protein kinase B; PKA: protein kinase A; TCA: tricarboxylic acid.

In response to low blood glucose concentrations, glucagon is released from α-pancreatic islet cells and promotes glucose production by stimulating gluconeogenesis and glycogenolysis, mainly in the liver. In the study by McDonald et al. (2021), glucagon levels in SOD1^{G93A} mice were reported to be elevated following a fast, and in response to insulin-induced hypoglycemia with minimal change to the overall blood glucose level. The observed increase in glucagon levels was also found to be independent of both glucagon secretion capacity and content in α-cells. This increase in glucagon level suggests that downstream glucagon signaling pathways may be impaired and glucagon insensitivity may contribute to aberrant glucose homeostasis. Another possible explanation for this elevation may be explained by the lack of suppressive effects of insulin on α-cell's glucagon secretion (**Figure 1B**). The intra-islet action of insulin has been suggested to stimulate an inhibitory effect on glucagon secretion through the PI3K/AKT pathway by promoting the phosphorylation and translocation of $GABA_A$ receptors to the cell surface of α-cells and thereby dampening secretion of glucagon (Xu et al., 2006). Hence, a decrease in insulin and its signaling pathway found in ALS would ineffectively suppress glucagon secretion in response to glucose stimulation, resulting in abnormally high levels of glucagon. There are still limited studies investigating the glucagon pathology in ALS, and as such, whether glucagon α-cells are driving dysregulated glucose homeostasis in this disease warrants further investigation.

In addition, excess glucose can be stored as glycogen by glycogenesis and can later undergo glycogenolysis to generate glucose-6-phosphate as an alternative fuel source when glucose becomes scarce. In ALS, increased levels of glycogen accumulation have been reported in both the spinal cord and skeletal muscle of $SOD1^{G93}$ at the onset of disease and ALS patients (Palamiuc et al., 2015; Tefera et al., 2021). However, the mechanisms underlying glycogen accumulation and its contribution to disease progression in ALS remains an enigma, although studies have hypothesized the involvement of impairments in glycogenolysis and glycogenesis. Evidence for this comes from the reduced expression of glycogen phosphorylase and enhanced activity of glycogen synthase in both $SOD1^{G93}$ mouse models and ALS patients (Palamiuc et al., 2015; Tefera et al., 2021). Interestingly, McDonald et al. (2021) recently showed that aberrant accumulation of glycogen in the liver of $SOD1^{G93A}$ mice might be due to defective glycogen mobilization. Notably, two of three enzymes that govern the activity of pyruvate dehydrogenase complex, a group of enzymes that plays a role in the entry of pyruvate to the tricarboxylic acid cycle, were downregulated in the liver of $SOD1^{G93A}$ mice at symptomatic stage (McDonald et al., 2021). This suggests that glucose utilization from glycogen stores could be downregulated due to deficit in glucose oxidation that is present at early stages of disease. Consequently, this could lead to a change in energy substrate preference from glucose to lipid for the tricarboxylic acid cycle to sustain ATP production (McDonald et al., 2021). Moreover, an increase in insulin-independent glucose uptake observed in the liver and skeletal muscle of $SOD1^{G93A}$ mice at symptomatic stage may contribute to the marked increase in substrate for glycogen synthesis in which glucose is shunted into glycogenetic pathways, rather than used for immediate source of energy (McDonald et al., 2021). Taken together, increases in glycogen accumulation in ALS could be attributed to a reduced ability to mobilize energy from glycogen stores, and increased glucose uptake in metabolically active tissues, such as the liver and skeletal muscle. However, whether changes in glycogen metabolism exacerbate energy deficits and play a role in ALS pathogenesis will require further investigation.

Conclusion: There is increasing evidence indicating dysfunctions in glucose metabolism contribute to ALS disease progression. The recent study by McDonald et al. (2021) demonstrates that alterations to glucose homeostasis, accompanied by shifts in energy balance, become more prominent in later stages of the disease. Therefore, further investigation into these axes hold possible therapeutic promise for ALS and other neurodegenerative disorders where glucose metabolism becomes compromised.

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References

Dobrowolny G, Lepore E, Martini M, Barberi L, Nunn A, Scicchitano BM, Musarò A (2018) Metabolic changes associated with muscle expression of SOD1(G93A). Front Physiol 9:831-831.

Liu Y, Wang T, Ji YJ, Johnson K, Liu H, Johnson K, Bailey S, Suk Y, Lu YN, Liu M, Wang J (2018) A C9orf72-CARM1 axis regulates lipid metabolism under glucose starvation-induced nutrient stress. Genes Dev 32:1380-1397.

Manzo E, Lorenzini I, Barrameda D, O'Conner AG, Barrows JM, Starr A, Kovalik T, Rabichow BE, Lehmkuhl EM, Shreiner DD, Joardar A, Lievens JC, Bowser R, Sattler R, Zarnescu DC (2019) Glycolysis upregulation is neuroprotective as a compensatory mechanism in ALS. Elife 8:e45114.

McDonald TS, Kumar V, Fung JN, Woodruff TM, Lee JD (2021) Glucose clearance and uptake is increased in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis through an insulin-independent mechanism. FASEB J 35:e21707.

Palamiuc L, Schlagowski A, Ngo ST, Vernay A, Dirrig-Grosch S, Henriques A, Boutillier AL, Zoll J, Echaniz-Laguna A, Loeffler JP, René F (2015) A metabolic switch toward lipid use in glycolytic muscle is an early pathologic event in a mouse model of amyotrophic lateral sclerosis. EMBO Mol Med 7:526-546.

Pradat PF, Bruneteau G, Gordon PH, Dupuis L, Bonnefont-Rousselot D, Simon D, Salachas F, Corcia P, Frochot V, Lacorte JM, Jardel C, Coussieu C, Le Forestier N, Lacomblez L, Loeffler JP, Meininger V (2010) Impaired glucose tolerance in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 11:166-171.

Scaricamazza S, Salvatori I, Giacovazzo G, Loeffler JP, Renè F, Rosina M, Quessada C, Proietti D, Heil C, Rossi S, Battistini S, Giannini F, Volpi N, Steyn FJ, Ngo ST, Ferraro E, Madaro L, Coccurello R, Valle C, Ferri A (2020) Skeletal-muscle metabolic reprogramming in ALS-SOD1(G93A) mice predates disease onset and is a promising therapeutic target. iScience 23:101087.

Stallings NR, Puttaparthi K, Dowling KJ, Luther CM, Burns DK, Davis K, Elliott JL (2013) TDP-43, an ALS linked protein, regulates fat deposition and glucose homeostasis. PLoS One 8:e71793.

Steyn FJ, Ioannides ZA, van Eijk RPA, Heggie S, Thorpe KA, Ceslis A, Heshmat S, Henders AK, Wray NR, van den Berg LH, Henderson RD, McCombe PA, Ngo ST (2018) Hypermetabolism in ALS is associated with greater functional decline and shorter survival. J Neurol Neurosurg Psychiatry 89:1016-1023.

Tefera TW, Steyn FJ, Ngo ST, Borges K (2021) CNS glucose metabolism in amyotrophic lateral sclerosis: a therapeutic target? Cell Biosci 11:14.

Xu E, Kumar M, Zhang Y, Ju W, Obata T, Zhang N, Liu S, Wendt A, Deng S, Ebina Y, Wheeler MB, Braun M, Wang Q (2006) Intra-islet insulin suppresses glucagon release via GABA-GABAA receptor system. Cell Metabolism 3:47-58.

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