BRAIN UPDATE

Protein glycosylation and synaptic transmission: brain glycogen keeps them separated

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Brain glycogen has long been regarded uniquely as a source of energetic support in situations of emergency or heightened activity. Recently, brain glycogen was found to contain a significant amount of glucosamine, which is used to sustain protein glycosylation.

In this update, we highlight that glucosamine synthesis through the hexosamine pathway would subtract glutamine, which is indispensable for glutamate and GABA recycling. Brain glycogen seems then to serve an additional role. By providing glucosamine and, through it, inhibiting the hexosamine pathway, glycogen avoids glutamine depletion.

In neurological glycogen storage diseases, the short-circuit between the hexosamine pathway and neurotransmitter recycling can cause epileptic seizures, which are the most common acute manifestation in these pathologies.

We finally discuss the metabolic and symptomatic superposition of glycogen storage diseases with congenital disorders of glycosylation, concluding that treatments ameliorating the clinical symptoms in some of the discussed pathologies could also be beneficial in others.

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Introduction

The human brain contains about 1 g of glycogen (0.1% of brain tissue weight), a 10 times lower concentration than in skeletal muscles and 100 times lower than in the liver.[1] Its turnover in the brain is, however, much more dynamic and continuous than in the other tissues where glycogen is abruptly used/restored upon necessity (intense exercise in muscles) or more slowly degraded/synthesized following the daily eating/fasting cycles (for blood glucose homeostasis in the liver). This pairs with two additional brain peculiarities:

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constant and expensive activity, and glucose as the almost exclusive energy source. Indeed, the brain has substantial energy demands, accounting for about 20% of the body's oxygen consumption and 25% of its glucose intake and ATP consumption, despite making up just 2% of total body mass.[2] The primary contributors to these high energy requirements are the maintenance and restoration of ion gradients disrupted by signalling processes, such as postsynaptic and action potentials, as well as the uptake and recycling of neurotransmitters. Of these, synaptic potentials, rather than action potentials, represent the most significant energy expense for sustaining excitability.[3]

Such a heavy and continuous glucose exploitation does not allow its peaceful storage into glycogen, which then never accumulates in brain cells over a minimal quantity in physiological conditions. Nonetheless, brain glycogen is fundamental. It is used in a liver-like mode, being mobilized during hypoglycaemia to locally compensate for the inadequate level of glucose (or in emergency following an ischaemic event with compromised blood flow and nutrient supply) and restored once normoglycaemia is reached (or following reperfusion).[4,5] However, glycogenolysis also occurs in normoglycaemic conditions, emphasizing other roles.[6] Indeed, brain glycogen is additionally used in a muscle-like mode to support neurons during periods of heightened activity. This hectic brain-specific hybrid glycogen usage is required for neurotransmission, cognitive functions, learning and memory formation[7,8] with a direct impact on their deterioration with ageing.[9-11]

A melting pot of glycogen modulators

Proteins governing glycogen metabolism in the brain constitute a fascinating mosaic. The oligosaccharide primer is synthesized by GYG2, the liver glycogenin,[12] and elongated by GYS1, the muscle glycogen synthase.[13] Glycogenolysis is instead mainly performed by the brain-specific glycogen phosphorylase (PYGB) [although the muscle glycogen phosphorylase (PYGM) is also minorly expressed in astrocytes, but not in neurons], the specific brain glycogen phosphorylase isoform, which, differently from PYGM and PYGL (liver glycogen phosphorylase), is sensitive to reactive oxygen species.[14-16] Additional regulators and cell-type differentially expressed isoforms complete the picture. Glycogenesis and glycogenolysis are oppositely regulated by various neurotransmitters and neuromodulators and by protein phosphatase 1 (PP1) dephosphorylation.[13-15] In the brain, PP1 is directed to glycogen metabolism by PTG (protein targeting to glycogen, aka PPP1R3C), exerting the role of G_M (muscle PP1 regulatory subunit, aka PPP1R3A) and G_L (liver PP1 regulatory subunit, aka PP1R3B), the insulin-activated muscle-specific and liver-specific subunits, but being insulin-insensitive. Indeed, brain glycogen (and glucose) metabolism is minorly affected by insulin[16,17]; this pairs with glucose transport occurring in the brain primarily by the insulin-insensitive transporters GLUT1, GLUT3 and SGLT1.

During embryonic development, glycogen can be detected in both neurons and glial cells, while in adults, it is almost exclusively synthesized in astrocytes.[18] The amount of glycogen correlates with astrocytic differentiation, with higher levels found in well-differentiated astrocytes. Astrocytic glycogen metabolism is highly dynamic. Indeed, glycogen can be rapidly converted to lactate through glycogenolysis coupled with glycolysis; lactate is then released for neuronal uptake in a process known as the astrocyte-neuron lactate shuttle (ANLS).[19] Or glucose can be directly offered to neurons [glucose-sparing by glycogenolysis (GSG)].[20] Glycogen granules are primarily localized within the astrocytic processes that are closely associated with synapses.[21] This strategic localization allows for rapid mobilization of energy substrates during synaptic activity. Neurons can then metabolize glucose or lactate derived from astrocytic glycogen to meet their energy requirements during periods of intense activity.

Glycogen metabolic machinery has also been detected in neurons, albeit in much smaller quantities than in astrocytes. Neuronal regulation of glycogen is less understood but appears to involve similar pathways. However, unlike astrocytes, the absence of glucose-6-phosphatase in neurons avoids the extracellular release of free glucose from stored glycogen; neurons use glycogen for their own functions and rely on astrocytic support for energy during high-demand situations.

How astrocytes cope with glycogen

Glucose stored in astrocytic glycogen can be directly donated to neurons via GSG or following glycophagy (glycogen autophagy), exported through GLUT1 (expressed in astrocytes) and imported via GLUT3 and SGLT1 (overexpressed in neurons).[22,23] Or, following glycolysis, it can be transformed into lactate by the astrocytic lactate dehydrogenase (LDH5, the muscle and liver isoform), which is then exported by specific monocarboxylate transporters, namely MCT1 and MCT4 (mainly expressed in muscles and working as high-affinity exporters); lactate is then imported by neurons through MCT2 (expressed primarily in the heart), oxidized to pyruvate by LDH1 (the myocardial isoform) and used for aerobic metabolism in mitochondria.[24] This mechanism resembles the increase in lactate usage by the heart during intense exercise when, utilizing lactate shuttling, the working muscles can fuel the beating heart.[25] The ANLS is crucial during intense neuronal activity when glucose availability may be limited. Neurons rely on astrocytic lactate to maintain ATP levels necessary for neurotransmission and synaptic function.[7,19,24-27] The ANLS also supports neuronal survival under stress conditions, such as ischaemia, by providing an alternative energy source that can be rapidly mobilized when blood flow is compromised. Consistently, astrocytes remove, through the glyoxalase pathway, the toxic methylglyoxal, an unavoidable by-product of glycolysis responsible for the formation of advanced glycation end products (AGEs).[28] Neurons are instead poorly protected and much more sensitive to methylglyoxal.

The hidden player in brain glycogen

In 2021, Gentry and colleagues demonstrated that in brain glycogen 25% of the saccharide units is glucosamine (GlcN, 1% and 0.1% in muscle and liver glycogen, respectively)[29]; GYS incorporates GlcN in glycogen using uridine-diphoshate-glucosamine (UDP-GlcN), while PYGB releases glucosamine-1-phosphate (GlcN-1P) from glycogen. Through the hexosamine biosynthesis pathway, GlcN is transformed into the UDP-*N*-acetylglucosamine (UDP-GlcNAc) required for protein glycosylation. They further demonstrated that in two glycogen storage diseases (GSDs) characterized by poorly metabolizable glycogen, free GlcN and UDP-GlcNAc are significantly reduced, and protein glycosylation is severely affected. They finally concluded that brain glycogen is a GlcN cache for protein glycosylation.

However, there could be something more to account for the specific GlcN enrichment in brain glycogen. Here, we propose that this peculiarity is to reduce to a minimum the interference of the protein glycosylation pathway (and other GlcN consuming pathways, e.g. ganglioside biosynthesis) with the glutamine-glutamate-GABA shuttles (Fig. 1). Actively glutamate- or GABA-releasing neurons are

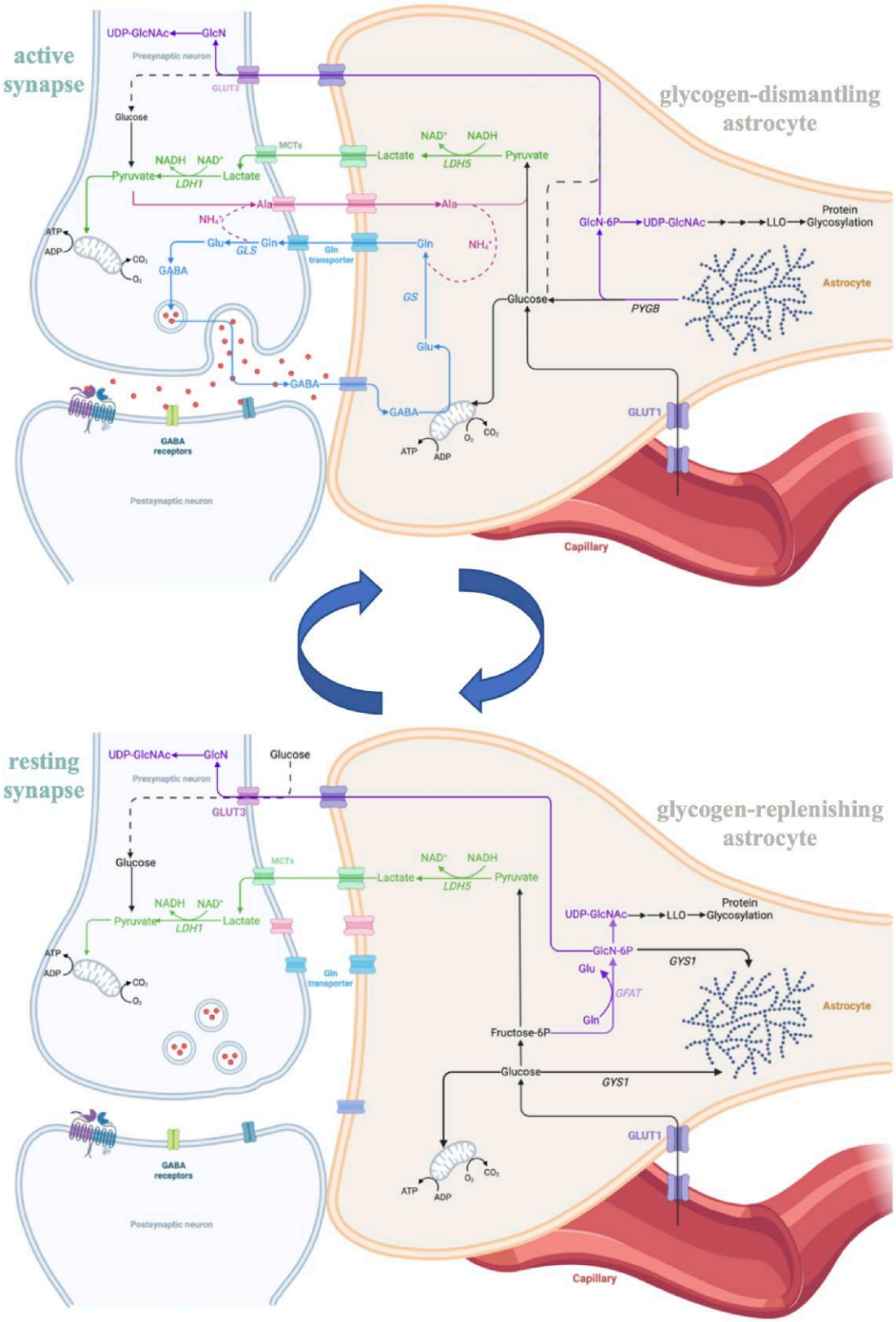

Figure 1 Management of astrocytic glycogen. Astrocytes sustain neuronal activity by providing glucose fuel for the increased energy demand, GlcN for protein glycosylation and glutamine for neurotransmitters restoration (*top*). Glycogen is then replenished via imported glucose and GFAT-synthesized GlcN-6P (*bottom*). GlcN = glucosamine; GFAT = glutamine-fructose-6-phosphate aminotransferase; GlcN-6P = glucosamine-6-phosphate; UDP-GlcNAc = UDP-N-acetylglucosamine; LLO = dolichol lipid-linked oligosaccharide; GLUT1 = glucose transporter I; GLUT3 = glucose transporter 3; PYGB = brain glycogen phosphorylase; LDH1 = lactate dehydrogenase 1; LDH5 = lactate dehydrogenase 5; GS = glutamine synthetase; GLS = glutaminase; MCT = monocarboxylate transporter; GYS1 = glycogen synthase 1. Created in BioRender. Lolli, G. (2025) https://BioRender.com/c7egrvx and https://BioRender.com/bdqh3d6.

supported by astrocytes replenishing glutamine and providing glycogen-derived glucose, lactate and GlcN.[30,31]In the recovery phase, astrocytic glycogen is reconstituted with glucose imported from blood vessels, and GlcN-6P is synthesized from fructose-6-phosphate and glutamine by glutamine-fructose-6-phosphate aminotransferase (GFAT). GFAT is regulated through feedback inhibition by UDP-GlcNAc; when glycogenolysis is active, the released GlcN-1P sustains UDP-GlcNAc production and GFAT inhibition.[32,33] In pathological conditions where glycogen support is deficient, glutamine is used for GlcN-6P production even when simultaneously requested for export to neurons; this results in an overall imbalance of the glutamine-glutamate levels in both astrocytes and neurons together with alteration of the connected ammonia detoxifying pyruvate-lactate-alanine cycle. GABAergic synapses will be more affected by glycogen unavailability considering the highest energy cost of the GABA shunt with respect to the simpler glutamine-glutamate cycle of the glutamatergic synapses. Indeed, the common manifestations in diseases affecting brain glycogen are developmental/cognitive impairment and drug-refractory seizures, a clinical sign of synaptic failures that could be ascribed at least in part to alterations in the glutamine-glutamate and glutamine-GABA cycles. Such failures and alterations are the hallmark of various neurological disorders associated with the malfunctioning of enzymes governing the interconversion of glutamine, glutamate and GABA, e.g. glutaminase, glutamine synthetase, glutamate decarboxylase (all causing various forms of developmental and epileptic encephalopathies)[34] and their recognition/transport. Interestingly, the same clinical manifestations are typical of congenital disorders of glycosylation (CDGs) comprising numerous diseases deriving from alterations in enzymes and proteins governing glycan synthesis and the associated trafficking mechanisms.[35]

Short-circuits in neurological glycogen storage diseases

The relevance of N-linked glycosylation in brain physiology and neurological disorders has been recently discussed, and its connection with glycogen metabolism has been touched on.[36] Here, we expand the net of the interconnected metabolic processes (Fig. 2). The emerging picture is that at least four main interdependent pathways influence each other in the brain, namely glycogen metabolism, glycolysis, protein glycosylation and neurotransmitter cycles. Alteration in any of these will affect the others, causing an overlap of clinical manifestations (developmental delay, cognitive and movement impairments, seizures) in various neurological disorders. Many other collateral pathways are also affected (e.g. ammonia homeostasis and pentose phosphate), which will not be further discussed here, although clearly contributing to the overall metabolic and symptomatic scenario.

The archetypal disease in this context is the GLUT1 deficiency syndrome (G1D).[37] Affected individuals suffer from reduced glucose uptake with the disease severity correlating with the impact of the single mutations on the transporter activity. Epilepsy appears in infancy/childhood accompanied by mild to severe psychomotor delay evolving into intellectual disability. Very recently, hyperexcitability in G1D has been connected to reduced GABAergic inhibition that was postulated to stem from the observed brain glycogen depletion.[38] Low levels of glucose affect the glycolytic process and the associated energy production. Ketogenic diets are used to treat G1D; seizure amelioration is due to increased energy fuel and partial carbon atom replenishment in the brain.[39] Considering the upstream role of GLUT1 in this context, protein glycosylation will also be affected, although no reports have investigated this aspect so far.

A similar scenario characterizes GSD0b, where GYS1 is mutated and glycogen synthesis is impaired. In the most severe form, patients present epileptic episodes and die of cardiac arrest in late childhood.[40,41] Protein glycosylation will be impacted by the missing GlcN release from the limited glycogen. The glutamine-glutamate and glutamine-GABA cycles will be consequently altered to try and compensate for GlnN production. Given instead the continuous glucose uptake, the energetic metabolism should only be minimally affected.

GSD7 is caused by phosphofructokinase (PFK) reduced activity. The most aggressive fatal infantile form is characterized by multisystem manifestations including seizures.[42] Here, the energetic production is obviously impaired (with a ketogenic diet being clinically beneficial in moderate forms of the disease) and glycogen builds up as a consequence of Glc-1P accumulation. Excess phosphohexoses feed the GlcN incorporation into glycogen and the hexosamine pathway, altering glutamine availability but possibly compensating toward a functional protein glycosylation.

Glycogen overaccumulation is also the hallmark of Lafora disease (LD), caused by mutations in either laforin or malin. The laforin/malin complex is responsible for the ubiquitination and the subsequent degradation of GYS and PTG.[43,44] In LD, active GYS continues synthesizing glycogen that accumulates in aberrant insoluble aggregates called Lafora bodies (LB). The first symptoms, jerky contractions and episodic epileptic attacks, appear in early adolescence. Seizures rapidly and dramatically increase in frequency and become drug-insensitive, accompanied by cognitive decline. Affected individuals generally die within 10 years from onset in a vegetative state and constant myoclonus. Glucose and GlcN availability is low due to their continuous incorporation in the poorly manageable LB accompanied by a significant reduction of N-linked glycans. LD clearly is both a GSD and a CDG,[29] although classified as neither. Similarly to G1D, the reduced availability of glucose and GlcN affects energetic production and glutamine/glutamate/GABA homeostasis.[45]

GYS1 uses UDP-glucose and UDP-GlcN as substrates to build up brain glycogen. These are synthesized by UTP-glucose-1-phosphate-uridylyltransferase (UGP2) mutated in Barakat–Perenthaler syndrome, an early infantile epileptic encephalopathy, lethal in the first years after birth and very similar to those reported as a consequence of mutated glutamine-glutamate-GABA interconverting enzymes. Barakat–Perenthaler syndrome is both a GSD and a CDG[46]; similarly to GSD0b, energetic metabolism should be minorly affected.

The picture is comparable moving to the previous metabolic step. The interconversion of Glc-6P and Glc-1P (and most probably of GlcN-6P and GlcN-1P) by phosphoglucomutase I (PGM1) bidirectionally connects glycolysis and glycogen metabolism. PGM1 deficiency causes GSD14, also known as CDG type 1T, a disease characterized by a wide range of clinical manifestations and severity, with neurological symptoms including seizures in > 40% of patients.[47] Neurological symptoms are present in other multisystemic GSDs, although with minor prevalence or impact and a later onset (adult polyglucosan body disease, Pompe disease and Cori disease), possibly connected to a partially retained brain glycogen usage (malfunctional glycogen-branching enzyme, acid-alpha glucosidase and glycogen-debranching enzyme, respectively).[48]

While in neurological GSDs protein glycosylation is often affected, only a minority of CDGs are associated with glycogen accumulation. CDGs are a heterogeneous group of more than 130 diseases defective in neurotransmission as most of the involved receptors and channels are N-linked glycoproteins that are retained in the intracellular

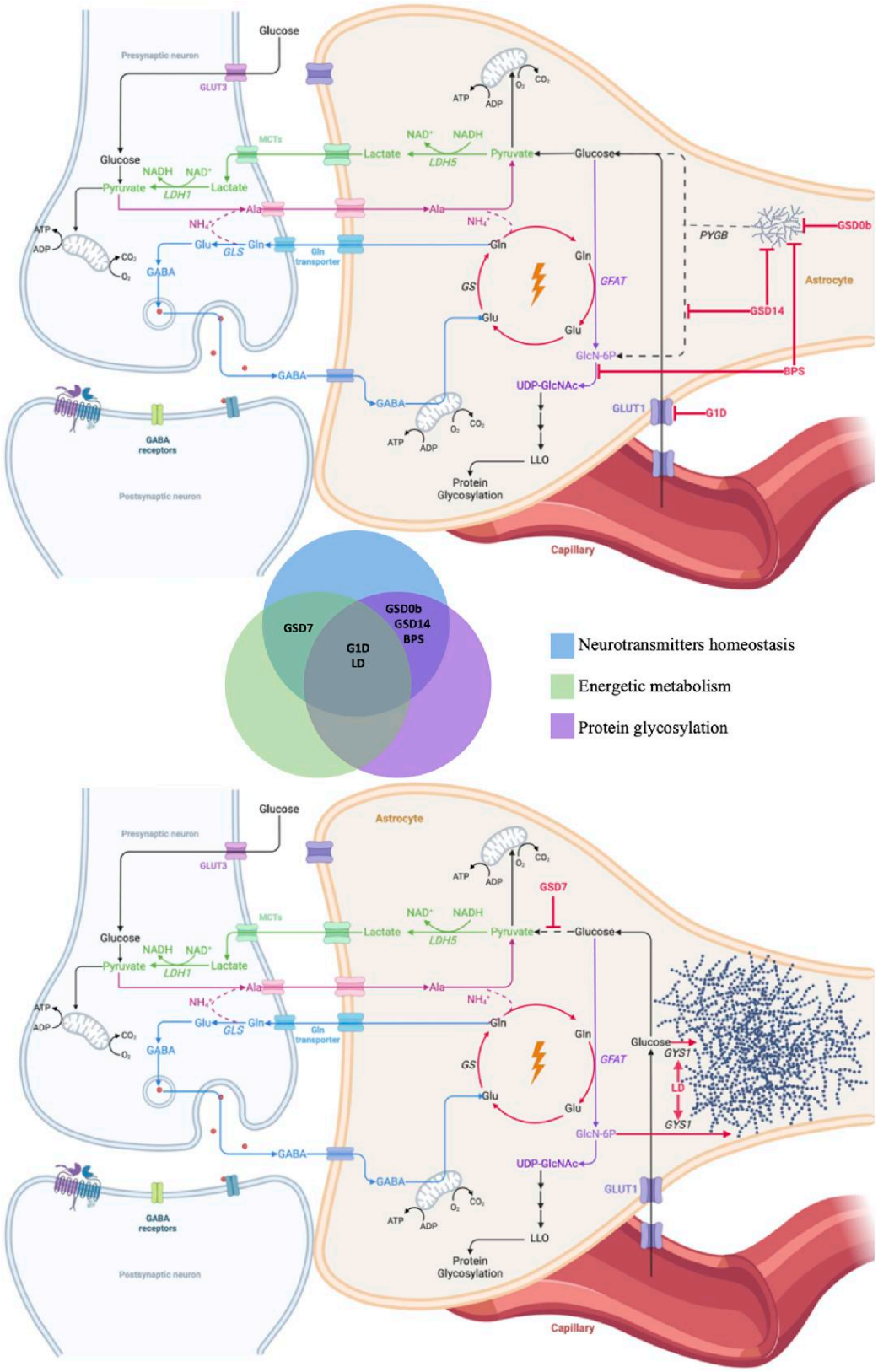

Figure 2 Short-circuits in neurological glycogen storage diseases. Alterations in the interconnected metabolic pathway are depicted for glycogen-depleting (*top*) and glycogen-accumulating diseases (*bottom*). GFAT = glutamine-fructose-6-phosphate aminotransferase; GlcN-6P = glucosamine-6-phosphate; UDP-GlcNAc = UDP-*N*-acetylglucosamine; LLO = dolichol lipid-linked oligosaccharide; GLUT1 = glucose transporter I; GLUT3 = glucose transporter 3; PYGB = brain glycogen phosphorylase; LDH1 = lactate dehydrogenase 1; LDH5 = lactate dehydrogenase 5; GS = glutamine synthetase; GLS = glutaminase; MCT = monocarboxylate transporter; GYS1 = glycogen synthase 1; LD = Lafora disease; G1D = GLUT1 deficiency syndrome; GSD0b = glycogen storage disease type 0b; GSD7 = glycogen storage disease type VII; BPS = Barakat–Perenthaler syndrome; GSD14 = glycogen storage disease type XIV. Created in BioRender. Lolli, G. (2025) https://BioRender.com/sakfk72 and https://BioRender.com/ervd4p9.

compartments when their glycosylation is impaired.[36] CDGs are divided into two main groups. Group I disorders are associated with defects in the assembly of the glycan precursor (LLO, dolichol lipid-linked oligosaccharide) and its transfer to proteins, while group II comprises alterations in the processing of the N-linked glycan in the endoplasmic reticulum and Golgi compartments.[49] In group I, only CDGs affecting the very first steps of carbohydrate channelling into the glycan biosynthetic pathway are associated with glycogen accumulation, with misdiagnoses reported.[50] Supplementation of specific monosaccharides/aminosaccharides/α-ketoacid sugars (galactose, mannose, fucose, GlcN, sialic acids) has proven beneficial in these CDGs with defects in the synthesis of the glycan precursors.[51-56]

The discussed superposition of metabolic alterations suggests that treatments ameliorating the clinical symptoms in one disease can be translated to some of the others. In treating LD for example, the ketogenic diet, already successfully employed for G1D and GSD7, could be introduced and supplemented with monosaccharides/aminosaccharides proven of satisfactory efficacy in some CDGs. This could slow down the disease course and possibly extend the efficacy of glutamate receptor antagonists (e.g. perampanel) or GABA receptor positive allosteric modulators (such as clonazepam) administered in LD, but progressively losing efficacy.

Neuron-glia alterations and regional vulnerability

GSDs are often seen as astrocyte-impacting diseases due to polyglucosan deposition in this cell type and only minor glycogen accumulation in neurons. On the other hand, CDGs are considered primarily neuron-centric because the most relevant symptoms (intellectual disability, seizures and ataxia) derive from aberrant neuronal development and function. GSDs and CDGs are instead pathologies affecting both neuronal and glial cells. As discussed above, neurological GSDs show aberrant protein glycosylation,[29] and their symptoms reflect those observed in CDGs. Proper glycosylation is required in neurons (neurotransmitter receptors, ion channels and synaptic adhesion proteins) but also indispensable in astrocytes for glucose uptake (GLUT1), neurotransmitter recycling (e.g. EAATs—excitatory amino acid transporters) and the ANLS (MCTs). In both GSDs and CDGs, dysfunctional glial cells, being unable to provide the correct metabolic support to neurons, certainly contribute to neuronal degeneration and the definition of the clinical symptomatology.

Clinical manifestations derive indeed from damage of specific brain areas. Brain regions with high synaptic density and plasticity have the greatest energy demand and require extensive and precise protein glycosylation.[57-59] Indeed, metabolic rate, synaptic activity and glycan decoration are all conjunctively elevated in the cerebral cortex, the hippocampus, the cerebellum and the thalamus. It is not surprising that glycosylation defects mirror the effects of energy deficits. Specifically, the cortex has the highest energy demand and extensive glycosylation of cell adhesion and synaptic proteins, and ion channels; in GSDs and CDGs, unsustained cortex requirements are responsible for severe and intractable seizures, cognitive decline and dementia. Similarly, the hippocampus relies on a continuous energy supply and GlcNAcylation for learning and memory.[60,61] GSDs and CDGs cause hippocampus damage, as also observed in recurrent hypoglycaemia, and symptoms quite superimposing to those observed in mesial temporal lobe epilepsy.[62] The cerebellum uses a significant amount of energy and depends on specific glycosylation for proper synaptic wiring in motor coordination; metabolic alterations result in ataxia and dysarthria. Finally, the thalamus has an intense energy demand for integrating, processing, and relaying motor and sensory information, being connected with all the above-mentioned brain regions; protein glycosylation is also fundamental for the proper functionality of the thalamocortical circuits, and thalamic damage is observed in GSDs and CDGs. The same four brain regions are the most susceptible to alteration of the Glu/GABA ratio and excitatory/inhibitory neurotransmission.[52,63] It is reasonable to suppose that GABA levels are more affected given the higher energetic cost of its recycling with respect to glutamate, resulting in hyperexcitability originating either directly in the cortex, the hippocampus or the thalamus or indirectly through the cerebellum (degeneration of the GABAergic Purkinje cells and excessively excitatory signals sent to the cortex and the thalamus).[64-67]

While the present discussion helps to explain the acute manifestations observed in GSDs and CDGs, it does not fully account for the progressive deterioration of the clinical picture, which is connected to the persistence of the above alterations ultimately ending in lysosome overloading, autophagy defects, overwhelmed unfolded protein response, ER stress and neuronal death. Their impact on GSDs, CDGs and many other neurodegenerative pathologies, including Alzheimer's and Parkinson's diseases, has been extensively reviewed.[36,68-70]

Discussion

Brain glycogen is absolutely peculiar in terms of amount, mobilization dynamics, distribution, usage, composition and regulation. Our knowledge about its characteristics has sensibly increased in recent years, derived mainly from studies on neurological GSDs. The incorporation of a sensible amount of GlcN in brain glycogen, the superposition of GSDs and some CDGs in terms of both metabolic and symptomatic features, and the acute manifestations in both pointing to synaptic failures indicate a fragile physiological balance and a delicate resource distribution among energetic metabolism, protein glycosylation and neurotransmitter recycling. Abrupt derailments from this thin track are typical of the above-discussed genetic disorders, while many observations suggest a slower divergence from it with ageing.

LD represents the best context to verify the proposed connections (and their alterations) of glycogen metabolism, protein glycosylation, the hexosamine biosynthetic pathway and synaptic transmission.[71] Indeed, LD mouse models were used to demonstrate that the missing release of glucose and GlcN from glycogen severely affects glycan decoration of membrane proteins in the brain.[29] Further experiments can be envisaged with the same model and in comparison with wild-type mice, either *in vivo* or *ex vivo* (synaptosomes). In particular, fluoroprobes could be used to stain recycling synaptic vesicles, and radiolabelled glutamate and GABA uptake could be measured in response to various treatments interfering with the hexosamine pathway or glycogen metabolism (i.e. the GFAT inhibitor azaserine, the cell-penetrating amylase fusion VAL-0417). Electrophysiological and complex spatial and temporal proteomic, metabolomic and glycomic studies can be designed to disclose a more comprehensive picture of the intricate relationship of these pathways in the brain.

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Competing interests

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