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Opinion

Sodium-glucose cotransporter-2 inhibitors: A potential novel treatment for Lafora disease?

Lafora disease (LD) is a recessively inherited neurological disorder characterized by progressive myoclonic epilepsy and cognitive and motor deterioration. It occurs worldwide with a relative higher frequency in Mediterranean countries (e.g., Spain, France, Italy), Northern Africa, the Middle East, and the Southern regions of India. LD can be considered an ultra-rare disease, taking into account the prevalence of less than 4 patients per 1,000,000 individuals [1]. Symptoms occur between 10 and 11 years of age, and life expectancy is about 10 years from the time of diagnosis [2–5]. At the current knowledge, LD is caused by recessive mutations in two genes: EPM2A, encoding laforin, a glucan phosphatase, and EPM2B/NHLRC1, encoding malin, an E3-ubiquitin ligase that regulate glycogen metabolism. Indeed, dysfunctions of laforin or malin causes glycogen accumulation (the so-called Lafora bodies) in various tissues, especially in neurons and astrocytes, leading to rapid neurodegeneration [1,6,7]. There is no effective therapy able to restore glycogen metabolism and halt or slow the progression of the disease [1]. The initial symptoms of seizures and epilepsy are treated with regular antiseizure medications (ASM), such as valproate, but patients soon become resistant to them. Besides valproate, other medications include topiramate, ethosuximide, phenytoin, phenobarbital, zonisamide, felbamate and benzodiazepines [2]. Symptomatic treatments include also ketogenic diet, trehalose as well as metformin [8–10]. Enzyme- and oligonucleotide-based therapies aimed at reducing glycogen accumulation, despite promising, are still under investigation and their approval will likely require some years [2]. Due to limited benefit and access to available options in the face of rapid progression of the disease, new pharmacological targets and new drugs must be investigated in the attempt to provide an early treatment to LD young patients. In this context, drug repositioning strategies could allow to identify “old” drugs (i.e. drugs already in clinical use) for “new” therapeutic indications, thus reducing time and cost of drug development, as happened for metformin in epilepsy and LD [9].

In the context of LD, the metabolic control of epilepsy and neurodegeneration can represent a promising basic-translational research ground for drug repurposing. Indeed, a complex bidirectional relationship has been highlighted between altered cell excitability and metabolic dysfunction. Abnormal excitability can be either the cause or the consequence of a metabolic disorder, in a vicious self-reinforcing cycle [11]. Some forms of epilepsy are in fact caused by mutations in genes that encode for key enzymes in glucose metabolism or for mitochondrial proteins [12], and LD itself is a form of progressive myoclonic epilepsy caused by alteration in glycogen metabolism. Further supporting the underlying metabolic disorder in epilepsy is the demonstration that the ketogenic, low-carbohydrate diet, or medium-chain fatty acid diet, are the only effective approaches in refractory cases of epileptic syndromes, such as in Dravet syndrome and GLUT1 deficiency, and also LD patients [13–15]. As a matter of fact, β-hydroxybutyrate and other ketone bodies proved several antiepileptic actions, including modulation of ion channels and transporters [11]. As mentioned above, metformin, a well-known drug licensed for the treatment of metabolic disease, has been repositioned, despite with questionable benefit, for LD treatment [8,10] and proposed for the treatment of neurodegenerative diseases [16], in view of its capability of correcting the perturbated energy metabolism associated to neuropathological conditions. In addition, some ASMs, including stiripentol (a modulator of GABAergic transmission and inhibitor of lactate dehydrogenase), owe their therapeutic action to mechanisms more complex than the classical ion channels related one, that include modulation of enzymes and of metabolic substrates formation [17].

1. The gliflozins’ hypothesis

In this scenario, a literature survey led us to suggest that sodium glucose co-transporter 2 (SGLT2) inhibitors, i.e., the so-called gliflozins, might be a potential therapeutic option in LD. These drugs initially developed and licensed for the treatment of type 2 diabetes mellitus (DMT2) are also currently approved for the treatment of heart failure and chronic kidney disease [18,19]. They act by blocking the SGLT2 expressed on the apical membrane of the proximal tubule of the nephron. SGLT2 and SGLT1 transporters enable glucose reabsorption by secondary active transport coupled to sodium transport. The Na^+/K^+-ATPase and the glucose transporters GLUT1 and GLUT2, on the basolateral membrane, contribute to sodium and glucose reabsorption to the blood. By blocking these transporters, glucose, sodium and water are removed from the body through urine. This mechanism ultimately reduces blood sugar levels [20]. Pharmacological blockade of SGLT2 results in the elimination of up to 80 g/day of glucose, lowering both fasting and postprandial blood sugar, without insulin intervention and thus without risk of hypoglycemia. Therefore, gliflozins (Table 1) are considered anti-hyperglycemic drugs, generally well tolerated, showing relatively limited side effects, such as an increased risk of developing ketoacidosis and urinary tract infections [21]. Moreover, through other diverse additional mechanisms, such as, for example, the improvement of redox state and vascular function, these drugs proven to slow the deterioration of renal function and to exert beneficial effects on cardiac dysfunction in patients with or without DMT2 [22]. Today, these drugs are also prescribed for the treatment of heart failure and chronic kidney disease, independently of the presence of DMT2 [18,19]. Dapagliflozin is the only drug in the family to have been approved for the treatment of diabetes even in children older than 10 years.

A body of experimental evidences supports the repositioning of gliflozins in the treatment of LD (Fig. 1), as detailed in the following paragraphs.

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Table 1
Gliflozins currently approved in Europe.

Brand name	Active compound
Ebymect	Dapagliflozin/Metformin
Edistride	Dapagliflozin
Forxiga	Dapagliflozin
Invokana	Canagliflozin
Jardiance	Empagliflozin
Synjardy	Empagliflozin/Metformin
Vokanamet	Canagliflozin/Metformin
Xigduo	Dapagliflozin/Metformin

2. Gliflozins and neuronal glucose and sodium reduction

The rationale behind the repurposing of gliflozins in LD is that the inhibition of the SGLT1/2 transporters by gliflozins could reduce glucose entry into neurons and astrocytes and consequently limit glucose storage into glycogen, thereby decreasing polyglucosan accumulation (LB formation) and slowing disease progression. Indeed, the SGLT1 and SGLT2 transporters are also expressed in the central nervous system. It has been shown that the SGLT1 transporter is expressed in brain areas including hippocampus (CA1, CA3, the dentate gyrus), cortical and cerebellar neurons, while significant expression of SGLT2 has been identified in the cerebellum and BBB endothelial cells [23,24]. Physiologically, SGLTs are electrogenic transporters, generating inward currents as they transport sodium across the cellular membrane, besides glucose. The concomitant movement of sodium can result in membrane depolarization and increased neuronal excitability [23]. Intriguingly, inhibition of SGLT1/2 could reduce sodium load in the brain, similar to what occurs in the kidney, and consequently reduce brain excitability mimicking the mechanism of action of commonly used ASMs sodium channel blockers. In addition, reduction of sodium entry-dependent depolarization can have beneficial effect in slowing down excitotoxic neurodegeneration by controlling chronic calcium entry and overload.

3. Gliflozins and ketogenesis

Gliflozins increase the production of ketone bodies (especially β-hydroxybutyrate) in patients with DMT2 [25], and ketone bodies, such as those from a ketogenic dietary regimen, have been shown to attenuate the frequency and severity of seizures in childhood refractory epilepsy [11]. The low-carbohydrate ketogenic diet works by mimicking the physiological phase of fasting, in which low carbohydrate levels induce hormonal changes (lowered insulin levels and increased glucagon levels) and stimulate the oxidation of fatty acids and the production of ketone bodies, especially β-hydroxybutyrate and acetoacetate, as an energy source. Ketone bodies provide a desirable and rapid source of energy for both brain and working muscles, irrespective of glycogen degradation. In addition, ketone bodies appear to have neuroprotective and antiepileptic action via different mechanisms, including increased

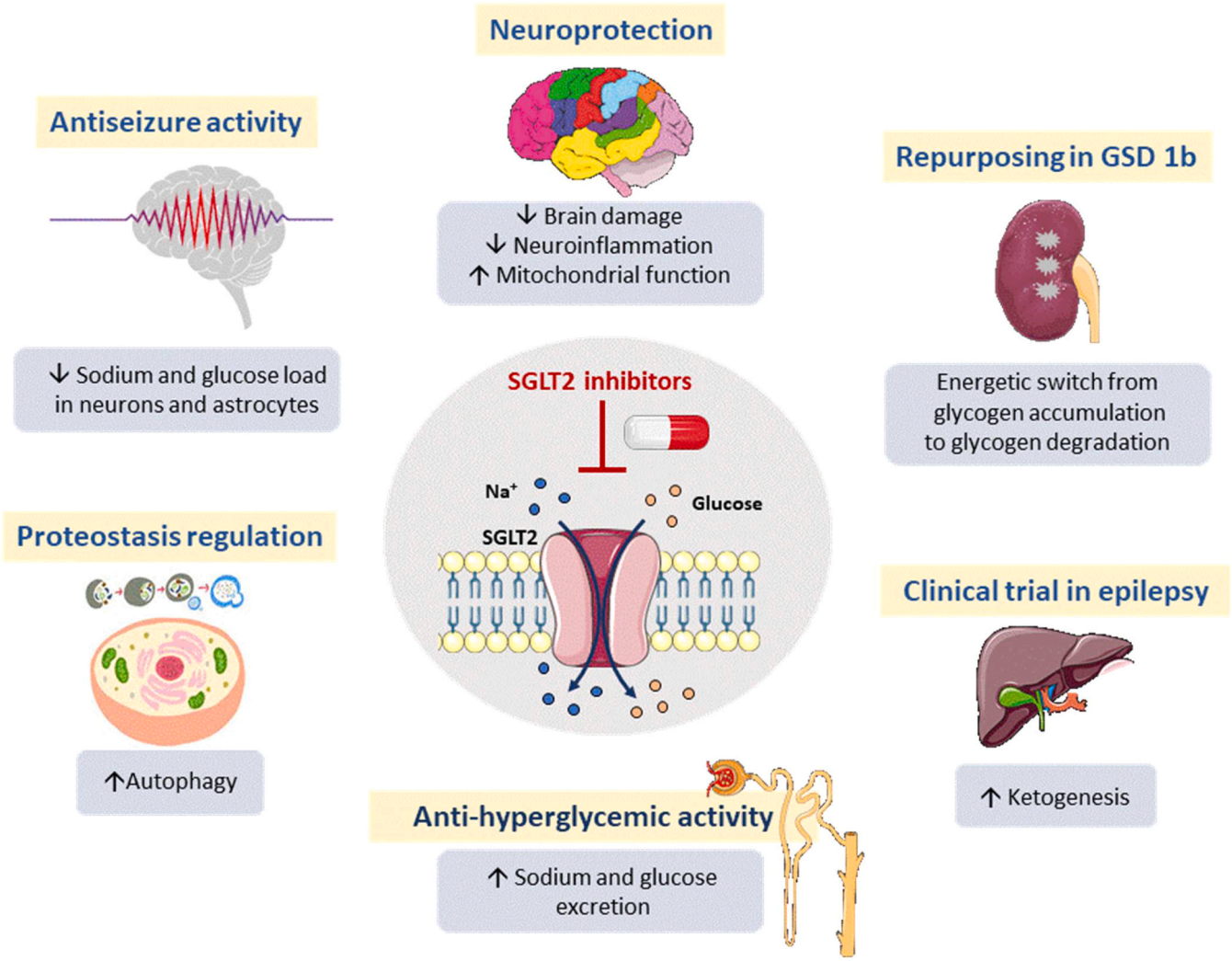

Fig. 1. Pleiotropic effects mediated by gliflozins.

adenosine release, activation of ATP-dependent potassium channels and inhibition of AMPA receptors, activation of PPARγ receptors with anti-oxidant and anti-inflammatory activity, downregulation of mTOR, and restoration of mitochondrial activity and DNA methylation pathways [11]. In the setting of LD, gliflozins could therefore mimic and have similar metabolic potential to that of a ketogenic diet. These drugs would shift normal glucose-based brain metabolism to fatty acid-based metabolism by promoting the synthesis and utilization of neuro-protective ketone bodies thus possibly reducing seizures susceptibility. In support of this hypothesis, dapagliflozin has been shown to reduce episodes of epilepsy induced by PTZ administration in an animal model of epilepsy [26]. In addition, a phase-1 clinical trial in 18 adults (NCT05512130) is underway to test whether gliflozins induce ketosis and can be used safely in adults for the treatment of epilepsy. The study, sponsored by Washington University School of Medicine, proposes the assessment of plasma β-hydroxybutyrate levels, blood glucose, and adverse effects during empagliflozin administration as primary outcome. The secondary outcome is the assessment of change in seizure frequency (https://clinicaltrials.gov/study/NCT05512130?cond=Epilepsy&term=gliflozin&rank=1). Actually, in a mouse model of LD, ketogenic diet was able to reduce LBs and increase the inactive phosphorylated form of glycogen synthase [27]. On the other hand, the ketogenic diet was tested in a group of 5 patients with LD, but showed limited efficacy probably because treated individuals were already in advanced stage of disease [28].

4. Gliflozins and neurodegenerative diseases

Several studies have demonstrated the neuroprotective effects of gliflozins in animal models of Alzheimer's disease and cerebral ischemia [24, 29–33]. Several mechanisms have been proposed to explain the neuroprotective action of gliflozins in models of neurodegeneration such as reduction of levels of insoluble amyloid beta protein, inhibition of acetylcholinesterase, protection of cerebral microcirculation and the BBB, and reduction of markers of oxidative stress and neuro-inflammation [34,35]. It has also been proposed that gliflozins can restore circadian modulation of mTOR and restore the balance between mitophagy and mitochondrial biogenesis [36]. These properties may further support the therapeutic potential of gliflozins in counteracting cognitive decline and improving the pathogenesis markers described for LD.

5. Gliflozins and autophagy

One pharmacological approach for LD is based on improving autophagy using trehalose, an autophagy activator and GLUT1 inhibitor that can reduce the formation of misfolded protein aggregates in various neurodegenerative diseases. Trehalose has been successfully tested in animal models of LD. This molecule reduces seizure susceptibility in a mouse model of LD by improving proteostasis and neuroinflammation [27,37] and ameliorates motor performance and hyperexcitability in a zebrafish model of LD [38]. Due to a certain structural similarity to trehalose, gliflozins may share similar mechanism of action thus helping to restore the altered proteostasis described in LD models.

6. Gliflozins and glycogen storage disease

Remarkably, gliflozins have been proposed for repositioning in glycogen storage disease type 1b (GSD1b). This autosomal recessive disease is caused by a deficiency in the glucose-6-phosphate transporter (G6PT), which transports G6P from the cytoplasm to the endoplasmic reticulum where glucose-6-phosphatase (G6Pase) catalyses the hydrolysis of G6P into free glucose and phosphate [39]. Altered activity of the G6PT/G6Pase complex in the liver and kidney affects glucose homeostasis, impairing blood glucose release and leading to severe glycogen accumulation in these tissues. In addition, patients with GSD1b suffer

Table 2
Representative preclinical and clinical studies supporting the effects gliflozins in glycogen storage and neurodegenerative disorders.

Disease	Preclinical and clinical outcomes	Putative mechanisms of action and pathway involved	References
GSD type 1b	- Dapagliflozin improved kidney morphology and function in the GSD1b mouse model - Empagliflozin improved the clinical symptoms (in particular neutropenia/ neutrophil dysfunction) in GSD1b patients and showed a favourable safety profile	- Reduction of glycogen accumulation in the proximal tubule by promoting GP activity and the expression of GYS inactive form - Improved kidney function by upregulation of NHE3, SGLT2, GLUT2, and AQP1/2 transporters - Reduction of 1,5-anhydroglucitol (1,5AG) in patients'plasma	[39,40,42]
Epilepsy	- Dapagliflozin reduces seizure activity in PTZ-induced mouse model of epilepsy. - Ongoing clinical trial with empagliflozin in epilepsy patients (ClinicalTrials.gov ID NCT05512130)	- Possible reduction of glucose availability and of sodium transport across neuronal membranes - Possible induction of ketosis and increase in beta-hydroxybutyrate	[26]
Parkinson disease	- Dapagliflozin improved motor dysfunction in a rotenone-induced Parkinson's disease rat model	- Improved oxidative stress (Nrf2 signaling), apoptosis (PI3K/AKT/ GSK-3β), neuroinflammation (NF-kb and TNF-α)	[33]
Cognitive decline in Alzheimer disease and diabetes	- Canagliflozin improved memory dysfunctions in a scopolamine-induced rat model of cognitive defects - Dapagliflozin improved brain function and prevented cognitive decline in HFD-induced obese rats; - Inhibitors of SGLT2 reduced the accumulation of Aβ and tau in the cortical region of a T2DM mouse model (ADT2DM mice)	- AchE inhibition - Improved brain mitochondrial function, insulin signaling, apoptosis and inflammation (Bax/Bcl2 ratio and NF-kb signaling), hippocampal synaptic plasticity - Restoration of mTOR signaling	[29,30,34, 36]
Acute cerebral ischemia	- Empagliflozin reduced infarct size and enhanced neurobehavioral functions in a rat model of cerebral ischemia/ reperfusion	- Modulation of stroke risk factors by reduction of antioxidants, anti-inflammatories, and antiapoptotic mechanisms (suppression of neuronal caspase-3 protein and upregulation of HIF-1α/VEGF signaling)	[34]

GP, glycogen phosphorylase; GYS, glycogen synthase, PTZ, pentylenetetrazol; HFD, high fat diet

from neutropenia and neutrophil dysfunction, that causes an increased risk of life-threatening infections and development of autoimmune disorders such as inflammatory bowel disease [40]. Several studies have shown that treatment with empagliflozin can improve neutropenia and inflammatory bowel disease in adults and adolescents with GSD1b [40–42]. Interestingly, in an animal model of GSD1b, dapagliflozin reduces glycogen accumulation probably through inhibition of glycogen synthase and activation of glycogen phosphorylase and, in this way, improves renal function [39]. In addition, gliflozins promote renal elimination of 1,5-anhydroglucitol-6-phosphate (1,5AG6P), a noncanonical metabolite that inhibits glycolysis in neutrophils contributing to neutropenia. Recently, the SGLT2 inhibitor dapagliflozin has been shown also to improve kidney function in a mouse model of glycogen storage disease XI [43]. These studies support the use of gliflozins in LD that is indeed a form of glycogen storage disease.

In light of these experimental evidences and the relative safety of this class of drugs (Fig. 1, Table 2), evaluation of pre-clinical and clinical efficacy would be decisive to verify whether gliflozins can be repurposed in the treatment of LD.

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Carella Massimo: Conceptualization, Writing – original draft, Writing – review & editing. **Liantonio Antonella:** Conceptualization, Writing – original draft, Writing – review & editing. **d'Orsi Giuseppe:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Imbrici Paola:** Conceptualization, Writing – original draft, Writing – review & editing. **Altomare Cosimo Damiano:** Conceptualization, Writing – original draft, Writing – review & editing. **De Luca Annamaria:** Conceptualization, Writing – original draft, Writing – review & editing. **Nicolotti Orazio:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

In this commentary we propose and discuss the potential repurposing of Gliflozins for the treatment of Lafora Disease, an ultrarare neurodegenerative disorder characterized by glycogen accumulation with high unmet medical need. We greatly hope that our manuscript would fulfil the requirement and the interest in publication in Pharmacological Research.

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