■ Letter to the editor

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Nanotechnology may provide hope for patients with glucose transporter type 1 deficiency syndrome

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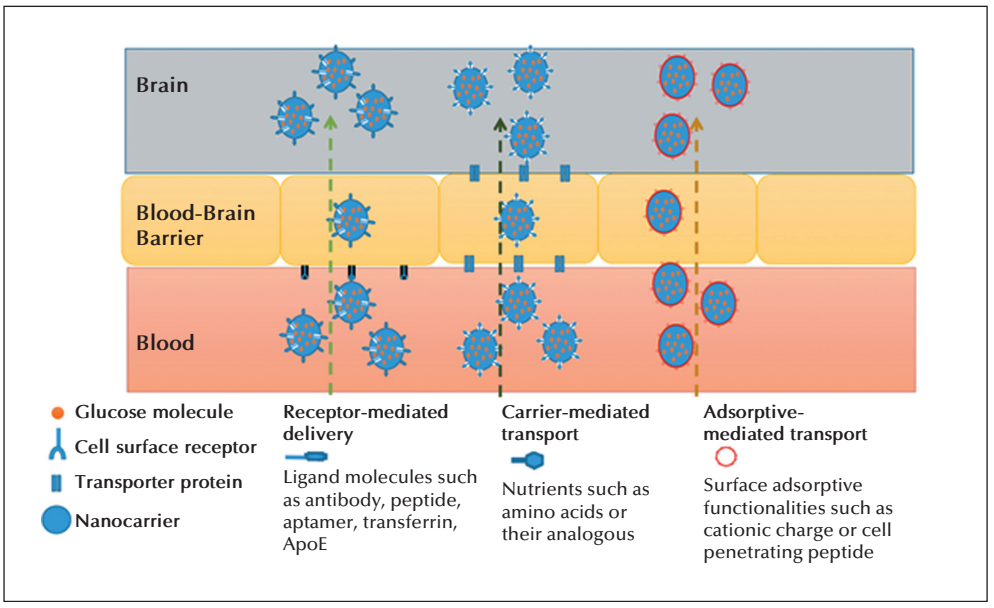
Glucose transporter type 1 deficiency syndrome (Glut1DS) is a genetic disorder of the cerebral energy supply system. Glucose transport across the blood-brain barrier (BBB) and astrocyte plasma membrane is exclusively made possible by glucose transporter type 1 (Glut-1) [1]. Patients with Glut1DS often present with drug-resistant epilepsy (with multiple seizure types) and deceleration of head growth during infancy; impaired development and complex movement disorders (*e.g.*, ataxia, dystonia, chorea, and tremor) may follow later. The prevalence of Glut1DS was estimated to be 1: 83,000 in Denmark and 1: 90,000 in Australia [2, 3]. The primary diagnostic procedure is a lumbar puncture showing low cerebrospinal fluid (CSF) glucose and low CSF lactate concentrations in the setting of normal blood glucose and normal blood lactate concentrations [1]. Hypoglycorrhachia in typical Glut1DS is defined as a cut-off value of 2.2 mmol/L (40 mg/dL). Milder phenotypes of Glut1DS may have CSF glucose values of 2.2 to 2.9 mmol/L (41 to 52 mg/dL) [1]. Currently, the only proven and approved therapeutic option for the treatment of people with Glut1DS is the ketogenic diet [4]. The ketogenic diet (KD) often controls seizures rapidly and effectively [1, 4]. The beneficial effects of the KD on the developmental delay and movement disorders may be significant, but appear to be less striking than that on seizures [1, 4]. Strict adherence to the KD is required for it to be most effective [1]. The ketogenic diet may have adverse effects in many patients. It has been associated with significant long-term adverse effects including osteopenia, hypercholesterolemia, liver steatosis, growth impairment, nephrolithiasis, and cardiovascular risks [1, 5]. Furthermore, it can be a very challenging and difficult therapeutic option [5]. As a result, not all patients with Glut1DS are on dietary treatment [4]. Therefore, easily applicable, well-tolerated therapeutic options with minimal adverse effects are critically needed for patients with Glut1DS.

The application of nanotechnology in medicine is called "nanomedicine". Nanomedicine has a potentially significant role in many medical fields, especially in the diagnosis and treatment of many diseases [6, 7]. Delivery of drugs or other therapeutic and diagnostic agents to different organs is one of the most quickly emerging areas of nanomedicine. Nanoparticles (NPs) may provide carriers that could deliver cargo to the target tissues or cells in a controlled manner [6]. Solubility enhancement of poorly soluble agents (*e.g.*, drugs), pharmacokinetic improvement for a controlled delivery, targeted delivery, high loading efficiency, and ability to pass the biological barriers (*e.g.*, BBB) make NPs excellent candidates as carriers. Many types of NPs have been used or suggested for delivery purposes [6, 7]. Glucose is normally being transported from blood to the brain via the carrier-mediated transport (CMT) pathway



■ **Figure 1.** Strategies that could be exploited for glucose delivery by nanoparticles to the brain.

(Glut-1 transporter protein). In patients with Glut1DS, glucose transport to the brain is disturbed [1, 8]. Nanoparticles could be engineered in a way that enable them to cross the BBB and deliver a cargo (*e.g.*, glucose) to the brain cells [9]. Considering the NPs' loading capacity, alongside their ability to cross the BBB, one could propose nanocarriers for glucose delivery to the brain in patients suffering from Glut1DS. *Figure 1* summarizes strategies that could be exploited for glucose delivery by NPs to the brain. A NP for glucose delivery to the brain must have a high loading capacity and good brain compatibility. Among various types of NPs that are used for brain drug delivery, vesicular lipid-based NPs (liposomes) may be appropriate candidates for the purpose of glucose transportation. Liposomes are bilayer lipid-based vesicles that are comprised of phospholipids and cholesterol with an aqueous core. Liposomes have excellent biocompatibility and biodegradability as their components (*i.e.*, phospholipids and cholesterol) enter the lipid metabolism system in the body. Lipid-soluble molecules could be loaded in the interface between the lipid bilayer, while the aqueous core provides a place for water soluble compounds (*e.g.*, glucose) [10]. Surface functionalization of liposomes is often indispensable in order to improve the blood circulation and brain-specific delivery; macromolecules (*e.g.*, polymers, polysaccharides, etc.) are usually used for this purpose. Cationic liposomes have shown to be more efficient carriers for the delivery of therapeutic drugs to the brain than conventional, neutral, or anionic liposomes, possibly due to the electrostatic interactions between the cationic liposomes and the negatively charged cell membranes, enhancing NP uptake by adsorptive-mediated endocytosis [10].

In conclusion, administration of a surface-modified glucose loaded cationic liposome could be hypothesized as a way for efficient glucose delivery to the brain in patients with Glut1DS. ■

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