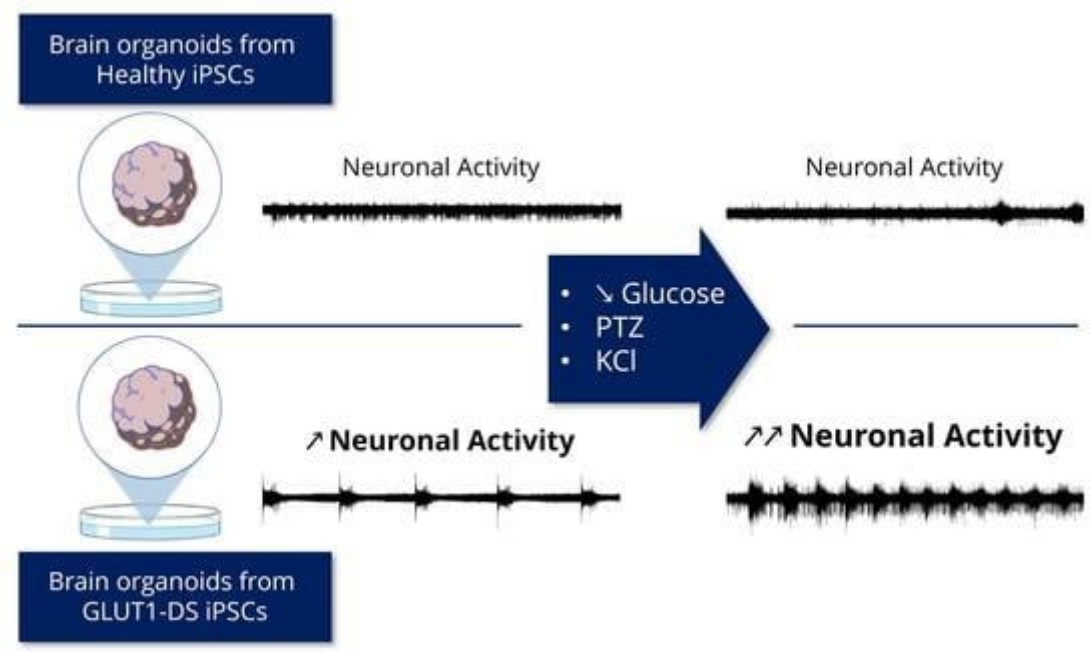

GLUT1-DSBrain Organoids Exhibit Increased Sensitivity to Metabolic and Pharmacological Induction of Epileptiform Activity

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Abstract Background/Objectives:

Glucose Transporter 1 Deficiency Syndrome (GLUT1-DS) is a neu rodevelopmental disorder caused by mutations in the gene encoding glucose transporter 1 (GLUT1), which leads to impaired glucose transport into the brain and is characterized by drug-resistant epilepsy. Limited glucose supply disrupts neuronal and astrocytic energy homeostasis, but how hypometabolism translates into network hyperexcitability remains poorly understood. Here, we used induced pluripotent stem cells (iPSCs)-derived brain organoids to examine how reduced metabolic substrate availability shapes epileptiform dynamics in human neuronal circuits from GLUT1-DS. Methods: Brain organoids were generated from a healthy donor or a GLUT1-DS patient and interfaced with multielec trode arrays (MEA) for recording of neuronal activity. A unified Python (v3.10)-based analytical pipeline was developed to quantify spikes, bursts, and power spectral density (PSD) across frequency bands of neuronal activity. Organoids were challenged with re duced glucose, pentylenetetrazol (PTZ), potassium chloride (KCl), and tetrodotoxin (TTX) to assess metabolic and pharmacological modulation of excitability. Results: GLUT1 DSorganoids exhibited elevated baseline hyperexcitability compared to healthy control, characterized by increased spike rates, prolonged bursts, increased spikes per burst, and elevated PSD. Reduced glucose availability further amplified these features selectively in GLUT1-DS. Conclusions: Human brain organoids reproduce the pathological coupling between hypometabolism and hyperexcitability in GLUT1-DS. Our platform provides a mechanistic model and quantification tool for evaluating metabolic and anti-epileptic therapeutic strategies

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