Decoding GLP-1: Digital Twins to Separate Neural Pathways From Metabolic Pathways in Brain Health

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GLP-1 receptor agonists are widely used to treat diabetes and obesity and are being investigated for potential cognitive benefits in Alzheimer's disease. However, these treatments simultaneously affect metabolic regulation and gut–brain neural signaling, making it difficult to determine which pathway drives cognitive outcomes. This study aimed to quantify the relative contributions of neural signaling and metabolic stabilization to cognition and to test whether GLP-1 signaling has a causal effect on brain health. A digital-twin simulation was developed to generate biologically realistic patient data in which treatment increased GLP-1 signaling. This signaling influenced two mediators: heart-rate variability and glucose stability. Multiple biological scenarios were simulated, and structural equation modeling (SEM) was used to estimate pathway-specific effects. Genetic triangulation was implemented using two-stage least squares with a simulated polygenic score and summary-level Mendelian randomization to validate causal relationships. SEM estimated pathway effects with high precision (MAE ˜ 0.036) and identified the dominant pathway in 76.7% of simulations. Accuracy reached 90% under moderate correlation but declined to 50% under high collinearity. Receptor sensitivity strengthened neural pathway effects. Genetic analyses showed positive signaling–cognition relationships with strong instrument validity ($F > 10$) and near-zero estimates under null conditions. This study demonstrates that a digital-twin framework can distinguish biological mechanisms and provides a scalable approach for improving the design of future GLP-1 clinical trials. It also establishes a reliable method for validating causal pathways under collinearity in complex human systems.

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