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Uncovering Off-Target Mechanisms of GLP-1R Agonists in Opioid Addiction via AI and Structural Systems Biology

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Glucagon-like peptide-1 receptor (GLP-1R) agonists, initially developed for type 2 diabetes and now widely utilized for weight management, have demonstrated potential impacts beyond appetite regulation and glucose metabolism, including possible effects on neurological reward and motivation centers associated with addiction. A significant cohort study revealed that semaglutide use is linked to a reduced risk of opioid overdose, though the mechanisms underlying this association remain to be elucidated. In this study, we leveraged recent advances in deep learning for biomolecular interaction prediction, such as AlphaFold3, to conduct an extensive off-target screening for GLP-1R agonists. The screening encompassed proteins linked to opioid addiction identified through a multi-omic, (including single-cell data) approach, including all human G-protein coupled receptors (GPCRs) and ion channels targeted by FDA-approved drugs. Our workflow involved comprehensive protein-protein interaction predictions, rigorous quality filtering of predictions, and detailed structural analyses to identify potential off-target interactions with semaglutide, dulaglutide, and tirzepatide. Central to our findings were interactions predicted with distinct targets for each drug, including the blockade of a critical region in a synaptic receptor that modulates adenylate cyclase activity, a key molecule in synaptic plasticity, thereby potentially influencing neurotransmission and reward signaling. To complement this structural systems biology approach, we plan to apply multiplex network perturbation techniques to predict how these interactions may propagate through networks related to substance use disorders, uncovering pathways that could reveal novel intervention points.