New method to predict the risk of adverse drug events

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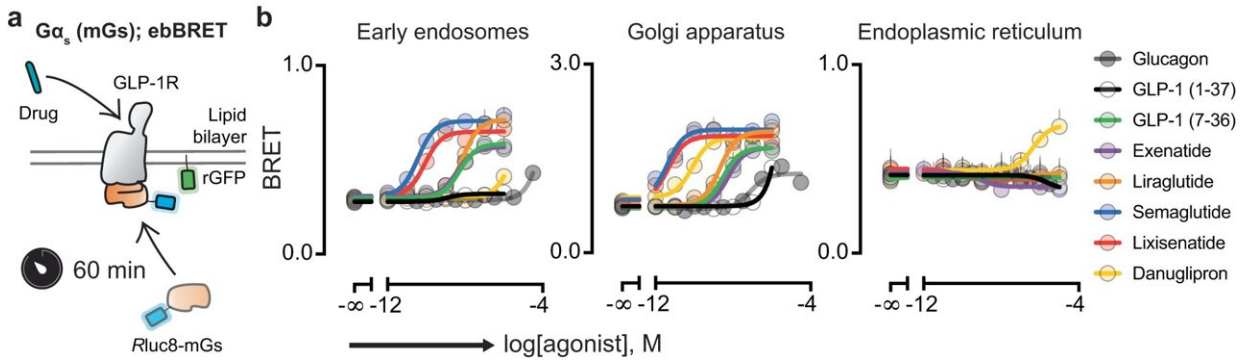

Stimulation of GLP-1R with peptide and small molecule agonists results in selective subcellular activation. **a** Schematic of the live cell experiment monitoring agonist-induced *R*luc8-mGs translocation to different cellular compartments where rGFP is expressed (EE—rGFP-FYVE; GA—tdrGFP-Giantin; ER—tdrGFP-PTP1B) based on BRET. **b** Concentration-response curves for G_s pathway activation of GLP-1R agonists at early endosomes, Golgi apparatus and endoplasmic reticulum. Data are represented as the mean ± SEM (n = 3 biologically independent experiments). EE early endosomes, GA Golgi apparatus, ER endoplasmic reticulum. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-41893-4

Studying signaling within cells can predict the risk of adverse drug reactions of novel obesity and type II diabetes treatments before they reach the patient, according to a new study from Karolinska Institutet published in *Nature Communications*.

Shane C. Wright, postdoctoral researcher at the Department of Physiology and Pharmacology, Karolinska Institutet, explains, "Our publication shows that drugs that bind GLP-1R—an important target for type II diabetes and obesity—change the shape of this receptor in different ways despite being developed to achieve the same outcome.

"Using biosensors, we show that these differences propagate throughout the cell, by changing the signaling proteins that interact with the drug -bound receptor and the subcellular compartment where this takes place (i.e., plasma membrane, endosomes, Golgi apparatus, endoplasmic reticulum).

"We compared the signaling profiles and the location of this activity which we call 'signaling neighborhoods' for a subset of anti-diabetic drugs and find that these correlate with adverse drug reactions reported to the U.S. Food and Drug Administration (FDA).

"These results are important because they may redefine the way that we explore the action of novel drugs and help guide our understanding of how to make new treatments with fewer side effects for patients.

"This was an international, multidisciplinary study that debuted a new suite of biosensors that can measure signaling in living cells with subcellular resolution (15 pathways in 4 cellular compartments). Together with comparative structure analysis, time-lapse microscopy and phosphoproteomics, we thoroughly characterized a subset of anti-diabetic drugs used in the clinics as well as a newer drug in clinical trials that is available in tablet form.

"We are increasing the number of drugs as well as the diversity of disease targets, which positions us for better predicting whether novel drugs will have a higher risk of adverse drug reactions before they reach the patient."

More information: Shane C. Wright et al, GLP-1R signaling neighborhoods associate with the susceptibility to adverse drug reactions of incretin mimetics, *Nature Communications* (2023). DOI: 10.1038/s41467-023-41893-4

Provided by Karolinska Institutet