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Structural Basis for a Bitter Taste Receptor Activation and its Potential Role in Targeting Diabetes

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ABSTRACT:

Background: Taste receptors are G protein coupled receptors that, besides being present in the taste buds, have also been shown to be present in the gastrointestinal (GI) system, respiratory system, and brain, though their function at these locations is not well understood.

Objective: To understand the nutrient mediated release of gut peptides like GLP-1 from enteroendocrine L cells of the GI system, we focused on a bitter taste receptor TAS2R38 (based on animal models) to investigate the structural basis of its potential role in the release of gut peptides.

Methods: The atomic-level structure of bitter taste receptor TAS2R38 was predicted using GEnSeMBLE, a first-principles based GPCR structure prediction method. These structures were obtained for the dominant taster haplotype (PAV) as well as for the nontaster haplotype (AVI) of the receptor. The known ligands phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PTU) were docked to these structures to provide a structural basis for the taster and nontaster haplotypes.

Results: Docking of known ligands PTU and PTC to taster and nontaster haplotypes of the bitter taste receptor showed a backbone hydrogen bond to residue 262 in taster but not in nontaster haplotype, suggesting a potential mode of action of these molecules in the activation of the bitter taste receptor.

Conclusion: These results combined with the ability of PTC to release gut peptides from in vitro models of the enteroendocrine L-cells, suggest a potential structural basis for TAS2R38 activation that can lead to the release of those peptides. This release has therapeutic benefit for type-2 diabetes and implies a role for bitter tasting (but safe) natural compounds targeting TAS2R38 as potential drug candidates for curing type 2 diabetes.

Key words: TAS2R38, GLP-1 release, PYY release, CCK release, enteroendocrine L cell, GPCR, protein structure prediction, GEnSeMBLE