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Bitter taste of Rebaudioside A from Stevia influences release of the gut hormone GLP-1 in human enteroendocrine cells

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Introduction: Rebaudioside A (Reb A), one of the main sweet constituents of the Stevia rebaudiana plant, is 300 times as sweet as sucrose, but also gives a prolonged bitter aftertaste. Intestinal entero-endocrine cells (EECs) release gut hormones related to appetite control, gut motility, and postprandial glucose homeostasis. Lately, it has been shown that Reb A stimulates the secretion of the gut hormone Glucagon-like peptide-1 (GLP-1) in pig intestines and mouse gut organoids. GLP-1 secretion is induced by activation of EEC expressed nutrient sensing G-protein coupled receptors (GPCRs), which respond to fatty acids, sweet-, umami- or bitter-taste compounds. Particularly, Reb A is known to interact with human bitter taste receptors TAS2R4 and TAS2R14.

Aim: study Reb A-induced GLP-1 secretion using the human EECs HuTu-80, and the role of bitter taste receptors as possible interaction mechanism.

Methods: Reb A and different sweet and bitter compounds were exposed to HuTu-80 cell monolayers for 2 hours. Total GLP-1 secretion was quantified in supernatants. Specific receptor involvement was studied by (pre-loaded) addition of blockers during exposure assays.

Results: Reb A-induced GLP-1 secretion was elicited dose-dependently from 0.15 - 1.5 mM (up to 2.3 fold-times, $P<0.001$). Sucralose and saccharin didn't induce GLP-1 secretion, while sucrose showed a small induction. The bitter compounds colchicine, 4-hydroxyanisol and flufenamic acid (ligands for TAS2R4 and TAS2R14) didn't induce GLP-1 secretion. Inhibition of TAS2R14 and TRPM5 did not reverse Reb A-induced GLP-1 secretion but GABA (blocker of TAS2R4) caused attenuation (20%, $P<0.05$), implicating TAS2R4 in Reb A-stimulated GLP-1 secretion.

Conclusion: Reb A induces GLP-1 secretion from HuTu-80 cells, unlike other sweet and bitter receptor-related compounds tested. Moreover, moderate inhibition of TAS2R4 suggests that secretagogue effect of Reb A on GLP-1 works partially via this receptor.