Endogenous peptide YY and Y1 receptors mediate FFA1 responses in mouse colon mucosa

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Long chain free fatty acids (FFAs) exhibit affinity for the FFA1 receptor and these nutrients are thought to have a physiological role in modulating energy homeostasis, in part by activating this receptor (which is also known as GPR40) [1]. FFAs trigger the secretion of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) from enteroendocrine L cells [2] and FFA1 is highly expressed in these incretin-secreting cells [3] as well as insulin-secreting pancreatic β cells [4]. Here we set out to establish the involvement of endogenous PYY and Y1 receptors in FFA1 activation using the FFA1 agonist GW9508 [5], the Y1 antagonist BIBO3304, in intact descending colon mucosa from wild-type (WT) and PYY-/- (KO) mice.

Changes in short circuit current (ΔI_{SC}) were measured under voltage-clamp conditions (see [6]). Mucosae from WT or KO mice were pre-treated with BIBO3304 (300nM) or vehicle (0.01% DMSO, basolaterally) and responses (in $\mu A.cm^{-2}$) to apical GW9508 (3 or 10μM) were recorded. Statistically significant differences ($P \leq 0.05$) were identified using one-way ANOVA with Bonferroni's post-test.

BIBO3304 revealed significant PYY-Y1 tone in WT mucosa (5.6 ± 1.1 $\mu A.cm^{-2}$, n=12) but not in KO tissue (0.9 ± 0.3 $\mu A.cm^{-2}$, n=11, $P < 0.001$). In WT tissue, GW9508 reduced I_{SC} in a BIBO3304-sensitive manner (Fig 1A) while BIBO3304 abolished residual GW9508 responses in KO colon (Fig 1B).

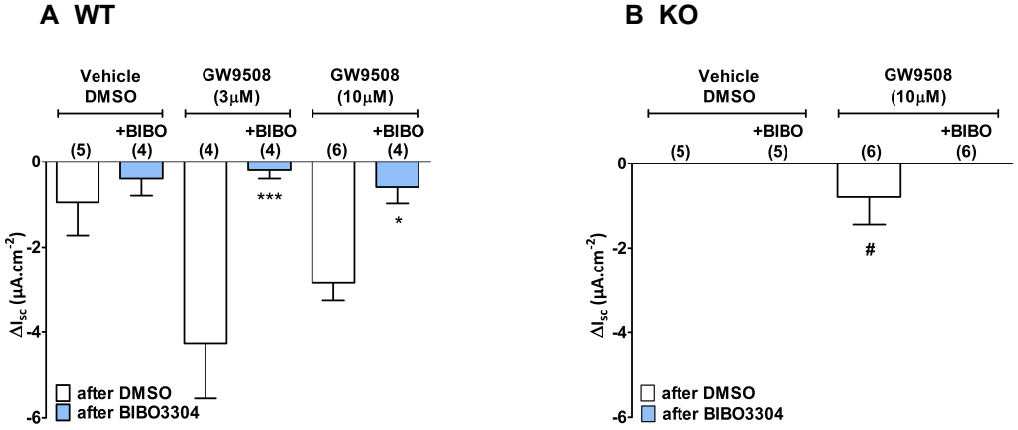

Fig 1: The effect of GW9508 ± BIBO3304 in WT (A) or PYY KO (B) mouse colon mucosa. Values are the mean -1SEM, * $P \leq 0.05$; ** $P \leq 0.01$ vs vehicle controls. # indicates $P \leq 0.05$ comparing WT vs KO data.

Apical GW9508 stimulated endogenous PYY release and Y1 receptor activation resulting in reductions in I_{SC} in WT, but not in KO colon. Y1 tone was also absent from KO tissue. We conclude that luminal colonic FFA1 activation triggers PYY-Y1 receptor paracrine inhibitory epithelial responses and suggest that this peptide may also contribute to slower intestinal transit [7] and to satiety. The FFA1 receptor is already a therapeutic target for Type 2 diabetes and obesity [8] and the agonist, TAK-875 is currently in phase 3 anti-diabetic trials. The co-release of PYY with GLP-1 should contribute to FFA1 agonist efficacy.

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