Colonic secretory currents induced by the pro-inflammatory cytokine, interleukin-6 is attenuated by bile acids.

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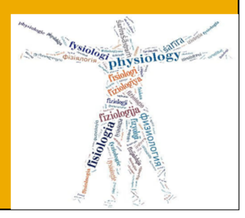

Introduction

- Hepatocytes synthesise and secrete primary bile acids (BAs), which are subsequently converted into secondary bile acids by intestinal microbes.
- In addition to facilitating lipid digestion and absorption, hepatic BAs also act as signaling molecules [1]. Their bioactivity is determined by whether or not they have been microbially modified and their conjugation status [2].
- BAs may act as cross-barrier signaling molecules that may modulate neural regulation of the intestine and secreto-motor activity [3].
- The aims of this study were to examine the effects of primary and secondary BAs on neuronal excitability in the submucosal plexus and explore potential interactions with the pro-inflammatory cytokine, interleukin-6 (IL-6).

Methods

- Fluorescent immunolabeling was used to investigate the localisation of G protein-coupled bile acid receptor 1 (GPBAR1, also called TGR5) and IL-6 receptors in cross-sections of colonic tissue from healthy Sprague Dawley rats.
- The possible neurostimulatory effects of primary and secondary BAs on submucosal neurons was assessed using calcium imaging.
- Modulation of baseline secretion of IL-6 from colonic tissue isolated in Ussing chambers by primary and secondary BAs was assessed using an enzyme-linked immunosorbent assay (ELISA) on the tissue secretions.

Results

TGR5 and IL-6 receptors are expressed mucosally and in enteric neurons

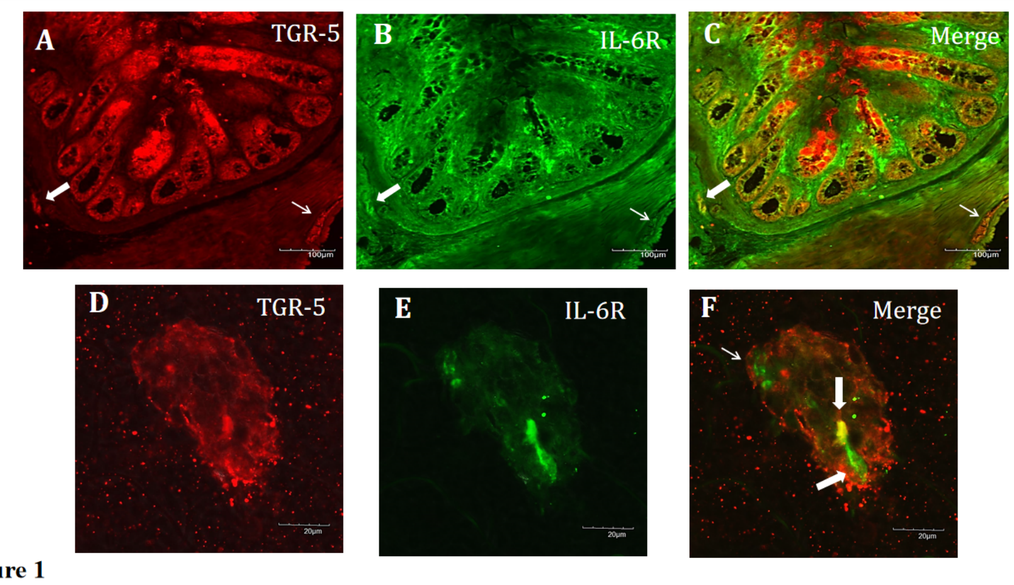

Figure 1
A: Immunofluoresecently-labelled colonic cross-sections reveal strong expression of the membrane-bound BA receptor, TGR5 on mucosal cells. Staining was also evident in neurons of the submucosal plexus (thick arrow) and the myenteric plexus (thin arrow). B: IL-6 receptors are expressed in the mucosa and muscularis and are C: co-expressed with TGR5 (merged image) in cells of the mucosal crypts and in enteric neurons. In whole mount preparations of submucosal neurons, weak TGR5 expression was evident in a punctate pattern on some but not all cells (D). E: IL-6 receptor expression was evident in some cells but F: little co-expression of the receptors was evident.

Concentration-dependent inhibitory effect of bile acids on submucosal neurons

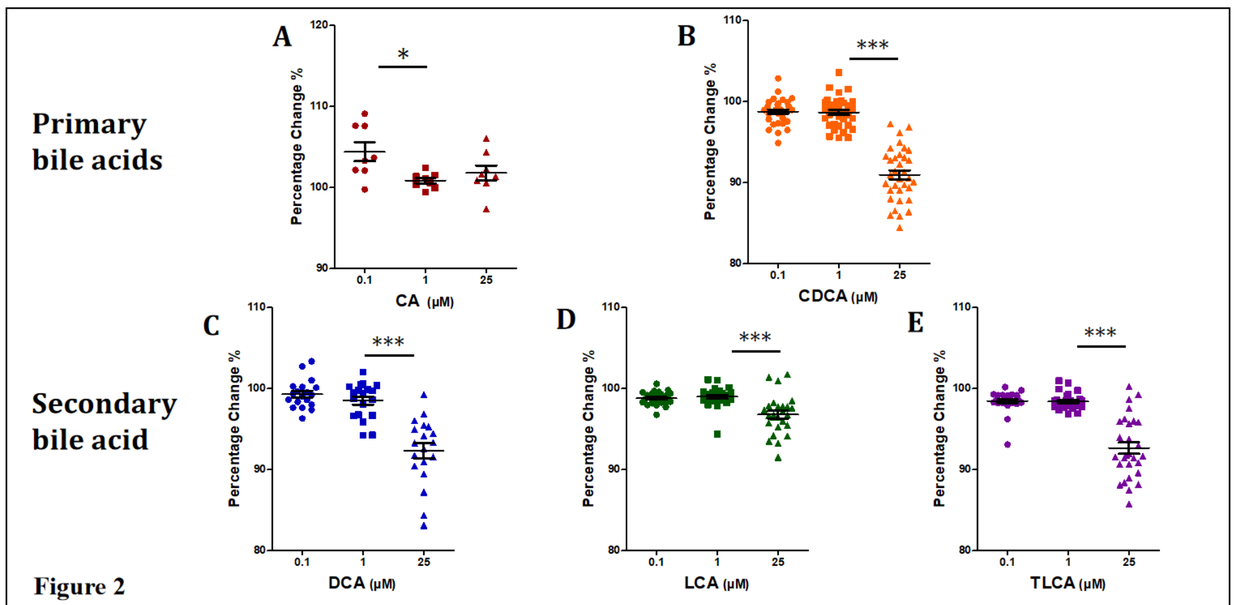

Figure 2
A: Basal intracellular calcium increased when exposed to the primary BA, cholic acid (CA) at a lower concentration (0.1μM), but didn't change at higher concentrations (1 μM and 25 μM). B: Chenodeoxycholic acid (CDCA,25 μM) suppressed intracellular calcium. C: The secondary BAs deoxycholic acid (DCA, 25 μM), D: lithocholic acid (LCA 25 μM) and taurine-conjugated LCA (TLCA, 25 μM) all suppressed calcium in the soma of submucosal neurons. Normalised data from individual neurons from at least three different SD rats is presented. * denotes p< 0.05 , *** denotes p< 0.001 (one-way ANOVA).

CDCA and TLCA suppress colonic secretion of IL-6

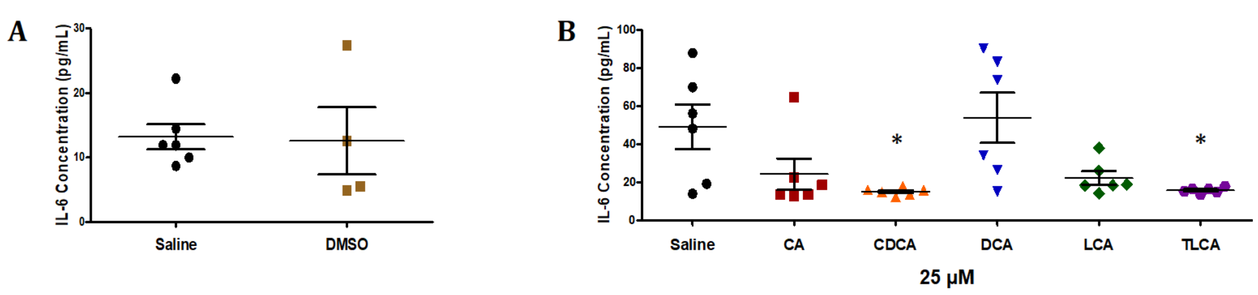

Figure 3
A: The mucosal side of colonic tissue mounted in Ussing chambers was exposed to bile acids (25 μM , 1 hour , room temperature). The secretions on the basolateral side was analysed for secretion of IL-6 using an ELISA assay. Exposure to saline and DMSO had no impact on basal secretion of IL-6. B: However, the primary BA, CDCA and secondary BA, TLCA suppressed basolateral secretion of IL-6. N=6 from 6 different SD rats. * denotes p< 0.05 (one-way ANOVA) .

Summary and Conclusions

- Consistent with the known anti-inflammatory effects of bile acids (4), one primary BA (CDCA) and the secondary BA, T-LCA suppressed basal colonic secretion of the pro-inflammatory cytokine IL-6.
- This effect may be neurally-regulated as CDCA and T-LCA also suppressed intracellular calcium in submucosal neurons, which regulate colonic secretory processes.
- Given that there is little evidence of co-localization of colonic TGR5 and IL-6 receptors, it is likely that this is mediated through an indirect effect of bile acids, however further experimental work will be needed to fully elucidate the signalling mechanisms underpinning these observations.

References

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