IN VITRO CELECOXIB SUPPLEMENTATION IMPACTS THE FUNCTIONAL CAPACITIES OF THE GUT MICROBIOTA

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Background

Alterations on inflammatory pathways lead to aberrant expression of cyclooxygenase-2 (COX-2) in colon carcinogenesis (CRC). The efficacy of COX inhibitors (coxibs) for successfully reducing CRC recurrence further confirmed the key role of COX-2. Alas, continuous COX-2 inhibition may increase the risk of a cardiovascular event. Currently, little information is available on how inter-individual variations in colon microbiota impact coxib disposition and overall celecoxib disposition.

Objectives

This project evaluated the effect of clinical concentrations of celecoxib on the *in vitro* colon microbiota. We determined the baseline microbiota activities and metabolic response, to reveal whether microbial drug metabolism impacts the conversion process.

Methods

We conducted *in vitro* batch culture experiments, assessing the potential of human faecal microbiota for metabolising celecoxib. Faecal slurries from four volunteers were supplied with 100 mg/ml of celecoxib and anaerobically incubated for 16h, to simulate the transit time of the proximal colon. Short-chain fatty acids (SCFAs) were considered benchmarks of gut microbial functionality and determined by gas chromatography. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to determine celecoxib recovery. Total RNA was applied to perform qRT-PCR of the bacterial 16S rRNA gene and to evaluate the metabolically active population.

Conclusions

Our results indicate that celecoxib shifts *in vitro* fermentation, in a donor-dependent manner. Celecoxib significantly decreased total SCFA and butyrate ($P < 0.001$), but not copy number of 16S rRNA gene in all donors. Microbial-derived SCFA, such as butyrate, may fuel proliferation of cancer-initiated epithelial cells. This study will provide information about the microbiota interplay on the efficacy of colon-targeted coxibs.