Reduction of trimethylamine N-oxide to trimethylamine by the human gut microbiota: supporting evidence for ‘metabolic retroversion’

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This is a copy of the poster presented at the ‘Exploring Human Host-Microbiome Interactions in Health and Disease’ conference, held at Wellcome Trust Genome Campus, Cambridge, UK, June-July 2015.

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**Reduction of trimethylamine N-oxide to trimethylamine by the human gut microbiota: supporting evidence for ‘metabolic retroversion’**

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**Introduction**

Dietary sources of methylamines such as choline, trimethylamine (TMA), trimethylamine N-oxide (TMAO), phosphatidylcholine (PC) and carnitine are present in a number of foods, including meat, fish, nuts and eggs. It is recognized that the gut microbiota is able to convert choline to TMA in a fermentation-like process (Fig. 1). Similarly, PC and carnitine are converted to TMA by the gut microbiota. It has been suggested that TMAO is subject to ‘metabolic retroversion’ in the gut (i.e. it is reduced to TMA by the gut microbiota, with this TMA being oxidized to TMAO in the liver). However, to date the role of the gut microbiota in TMAO degradation has not been investigated.

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**Methods**

Screening of bacteria for ability to reduce TMAO. Sixty-six strains of human faecal and caecal bacteria (in-house collection) were screened anaerobically for their ability to utilize TMAO using liquid minimal media with and without 1% (w/v) TMAO. Metabolites in spent media were profiled by Proton Nuclear Magnetic Resonance (1H NMR) spectroscopy.

**In vitro fermentation systems.** Anaerobic, stirred, pH-controlled, batch culture fermentation systems were performed using minimal broth with and without 1% (w/v) TMAO and inoculated with faecal homogenates prepared from freshly voided stool samples (three healthy human; one male, two females; age range 20–31). Samples were taken at 0, 1, 2, 3, 4, 5, 6 and 9 h for microbiological (fluorescence in situ hybridization; FISH) and metabolite (1H NMR) profiling.

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**Results**

**Screening cultures for TMAO reducense activity.** The presence of TMAO in media increased the growth rate of Enterobacteiraceae; while it did not affect the growth rate of lactic acid bacteria, TMAO increased the biomass of these bacteria (Fig. 2).

**Enterobacteiraceae** produced the greatest amount of TMA from TMAO (38.79 ± 11.08 mM [14.92–53.91 mM]; n = 20). Members of other families of bacteria produced low levels of TMA from TMAO (0.02–4.52 mM). Caecal/small-intestinal isolates of *Escherichia coli* produced more TMA from TMAO than their faecal counterparts (Fig. 3). Lactic acid bacteria (LAB) did not convert TMAO to TMA, but their production of lactate was greatly increased when they were grown in the presence of TMAO (Fig. 4).

**Effect of TMAO on gut bacteria within a mixed system.** Abundance of Enterobacteiraceae (probe Ent) significantly increased in the presence of TMAO. Enterobacteiraceae, n = 20; Bifidobacteriaceae, n = 7; Streptococcaceae, n = 5; *P* < 0.05.

**Conclusion**

**Enterobacteiraceae** made the greatest contribution to the conversion of TMAO to TMA, both in pure culture and in a mixed microbiota. This work clearly demonstrates different metabolic activity of strains of the same bacterial species from different gut niches.

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**References**


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