Exploring the Potential Short Chain Fatty Acid-Serotonin Axis in Irritable Bowel: Insights from an Integrated Faecal and Urinary Metabolomic Analysis

BACKGROUND

The extent to which individuals with irritable bowel syndrome (IBS) respond to the low FODMAP diet (LFD) has been linked with the colonic metabolome, specifically short chain fatty acid (SCFA) profiles. A faecal metabotype high in SCFAs can be manipulated by restricting FODMAPs and is associated with an enhanced clinical response. Whether these SCFA metabolites are themselves driving symptoms, or whether they are triggering downstream neuroactive metabolites via a SCFA-serotonin axis is unclear. We examined the urinary metabolome with the aim to gain further biological insight into this emerging IBS subgroup.

METHODS

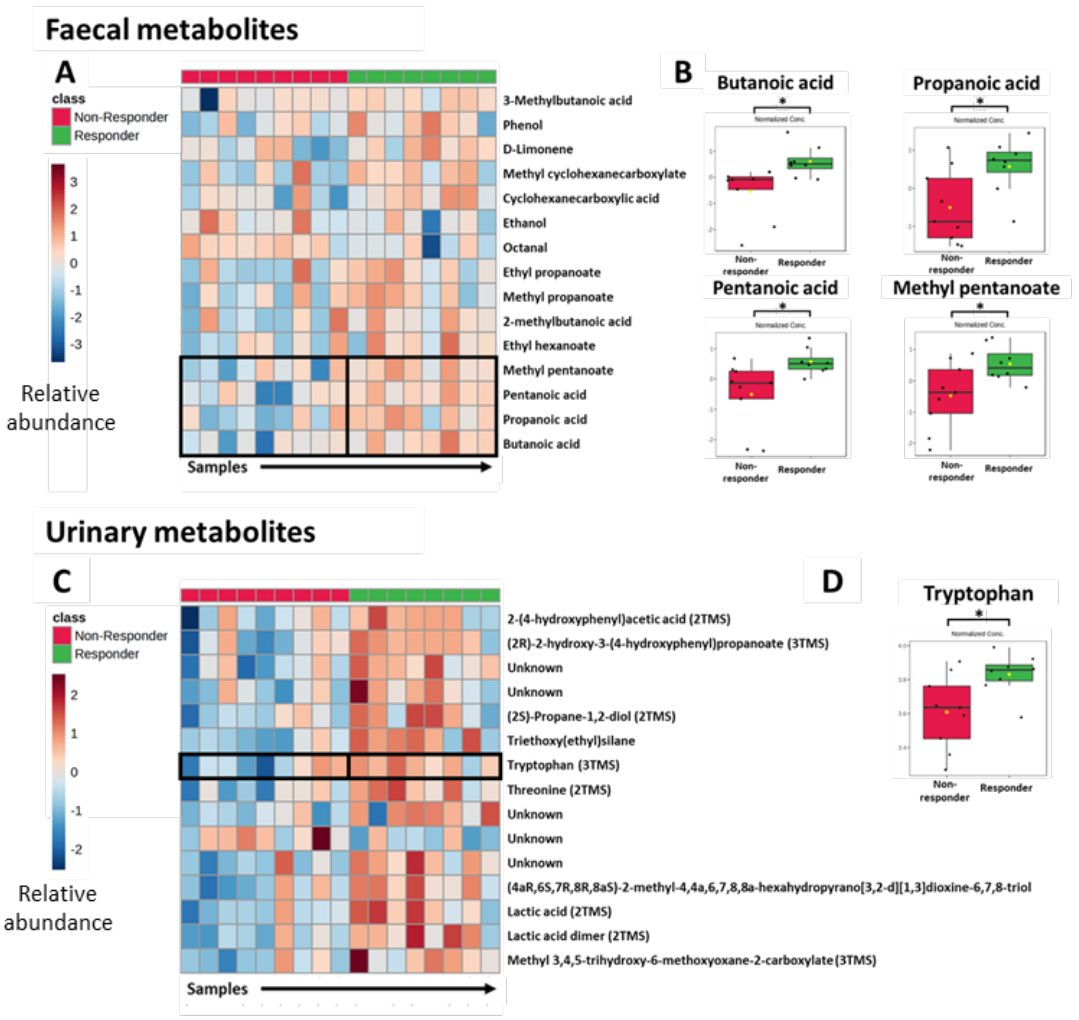
Faecal and urine samples were collected at baseline during consumption of a habitual diet from 17 patients with non-constipated IBS (Rome III). These patients then completed a 4-week dietitian supervised LFD – 8 were 'responders'. Baseline faecal samples were analysed with solid phase microextraction gas chromatography-mass spectrometry (GC-MS). Urinary samples were analysed using a chemical derivatization GC-MS method. Metabolite abundance was compared using an independent samples t-test.

RESULTS

Using hierarchical clustering, urinary metabolites clearly separated responders and non-responders at baseline. The responder urinary metabotype was characterised by a relative abundance of tryptophan (p<0.05), the precursor to serotonin. Faecal SCFAs characterised LFD responders at baseline and correlated strongly with urinary tryptophan and 5-HIAA (the primary metabolite of serotonin). Further, the faecal SCFAs correlated with other aromatic amino acids which share common origins with tryptophan.

CONCLUSION

The metabolic signature associated with LFD responsiveness in non-constipated IBS extends beyond the gut and can be detected in urine. The correlation observed between faecal SCFAs and urinary tryptophan/5-HIAA suggests that a potential SCFA-serotonin axis might underpin symptoms in IBS. Moreover, these findings suggest that the relief often experienced following FODMAP restriction might stem from the modulation of this axis.



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		Faecal metabolites				
		Acetic acid	Propanoic acid	Butanoic acid	Pentanoic acid	Methylpentanoic acid
Urine metabolites	5-HIAA	r -0.188^{ns}	r 0.307^{ns}	r 0.497*	r 0.189^{ns}	r 0.354^{ns}
	Tryptophan 3TMS	r 0.074^{ns}	r 0.598*	r 0.613**	r 0.231^{ns}	r 0.256^{ns}
	Tyrosine 3TMS	r 0.284^{ns}	r 0.293^{ns}	r 0.531*	r 0.241^{ns}	r 0.047^{ns}
	Phenylalanine 2TMS	r 0.017^{ns}	r 0.418^{ns}	r 0.705**	r 0.013^{ns}	r 0.416^{ns}

A. Heatmap demonstrating the top 15 most-significant fecal metabolites contributing to the differentiation of low FODMAP diet Responders from Non-Responders [* p<0.05]
B. Box and whisker plots of the relative abundance of 4 of the key fecal metabolites.
C. Heatmap demonstrating the top 15 most-significant urinary metabolites contributing to the differentiation of low FODMAP diet Responders from Non-Responders [* p<0.05]
D. Box and whisker plot of the relative abundance of tryptophan.
E. Correlation patterns observed between key faecal VOCs and key urinary metabolites; colour scheme – red denotes positive correlation (5-HIAA - 5-Hydroxyindoleacetic acid; ns – not significant; TMS – trimethylsilyl derivatives; * p<0.05; **p<0.01; r – Pearson coefficient).