Propionate has protective and anti-inflammatory effects on the blood–brain barrier

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Background
Composition and functions of the gut microbiota are inextricably linked with host health, and altered in conditions such as obesity, type II diabetes and cardiovascular disease. Evidence is accumulating to suggest the gut microbiota is also altered in neurodegenerative diseases. Central to microbial-host cross talk are microbiome-associated metabolites such as short-chain fatty acids (SCFAs). SCFAs are produced by the fermentation of carbohydrates and other foodstuffs by gut bacteria, are potent bioactive molecules and are detectable at micromolar concentrations in the peripheral blood of healthy individuals. They activate members of the free fatty acid receptor (FFAR) family of G protein coupled receptors; acetate, propionate and butyrate have affinity in the low millimolar to high micromolar range for FFAR2; propionate and butyrate have mid to low micromolar affinity for FFAR3.

Propionate has been shown to stimulate intestinal gluconeogenesis through direct stimulation of enteric–CNS pathways, and increased intestinal propionate has been associated with reduced stress behaviours and reward pathway activity in mice and humans, respectively. However, its potential role as an endocrine mediator in the gut–brain axis has not been addressed.

Methods
Immunohistochemistry to detect expression of FFAR3 in the human brain was done with paraffin-embedded post mortem samples of prefrontal cortex from non-neurological controls. Human hCMEC/D3 cerebro microvascular cells were used as an in vitro model of the BBB to investigate the effects of 24 h treatment with propionate, studying (i) expression of FFAR3 by cell monolayers, (ii) cell transcriptions, (iii) functional barrier properties of cell monolayers and (iv) Ap efflux transporters. Differentially expressed genes were identified in hCMEC/D3 transcriptomes using limma (significance threshold 0.1 after adjustment of P values for multiple correction testing, Benjamini-Hochberg). Signaling Pathway Impact Analysis (SPIA) and Enrichr were used to aid data interpretation.

Results
1. FFAR3 is expressed in the human brain and on hCMEC/D3 cells

2. Propionate has a significant effect on hCMEC/D3 cell gene expression, and inhibits pathways (SPIA) associated with non-specific microbial infections

3. Propionate protects the BBB against exposure to bacterial lipopolysaccharide via CD14, and enhances inter-endothelial tight junctions

4. Propionate protects the BBB from oxidative stress via NRF2 (NFE2L2) signalling

5. Exposure of hCMEC/D3 monolayers to propionate for 24 h significantly suppressed expression of LRP-1 (not shown) without modulating expression of either BCRP or P-glycoprotein

Summary
In vitro propionate has protective and anti-inflammatory effects on the BBB. There are currently three known mechanisms by which the microbiome influences the gut–brain axis: modification of autonomic/sensorimotor connections, immune activation, and regulation of neuroendocrine pathways. We propose a fourth facet of the gut–brain axis: interactions between microbiome-associated metabolites and the primary defensive structure of the brain, the BBB. This warrants further study.

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References

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