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Modelling of metabolic control by Short Chain Fatty Acids at the level of the functional proteome – II: *systems biology model of SCFA metabolism*

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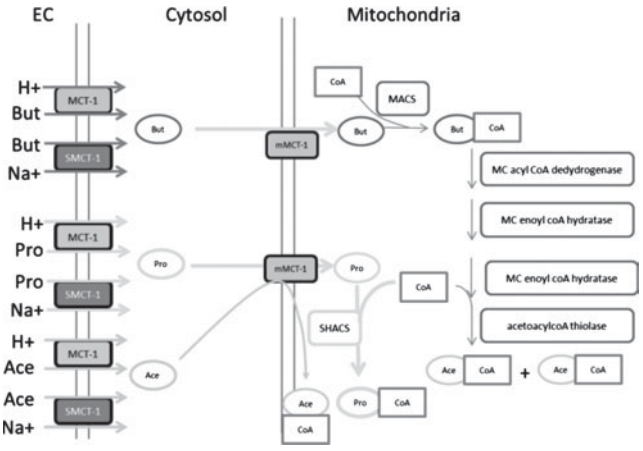
Background: Short-chain fatty acids are produced by microbial fermentation in the large bowel. SCFA produced may account for up to 10% of daily calorific need. SCFA are taken up into the colorectal epithelia by two transporters. Butyrate is metabolised to produce acetyl-coA and energy, but may compete for ligating enzymes and free coA-SH with propionate and acetate. In vivo these molecules may be exported to the blood, however we sought to generate a model representative of in vitro metabolism and management of SCFA.
Methods: Initially a q-NET was developed extending our published butyrate metabolic q-NET[(1)] with the additional of mitochondrial metabolic pathways for acetate, propionate and butyrate (Fig. 1). An outline model was constructed in Copasi. The model was parameterised by searching enzyme respositories (BRENDA), Pubmed and by backward and forward citation searches. The model was challenged with typical levels of acetate, propionate and butyrate found in the gut (25, 7 and 5 mM respectively) and 200 min timecourse simulations undertaken. The effect of deletion of SMCT-1, and of variation in levels of individual SCFA were determined.



Results: The simulations indicated microchondrial accumulation of SCFA, with propionate and butyrate equilibrating with the extracelular concentration, but not acetate, despite the excess concentration. Intramitochondrial acetyl-coA and coA-SH were depleted at the expense of other acyl-coA, in accordance with the published literature. Reduction in butyrate concentration drove increased intramitochondrial propionate, but paradoxically reduced intramitochondrial acetate. Increased butyrate reduced propionyl coA. Variation in extracellular acetate had no effect on intramitochondrial coA-SH or acyl-coA. Deletion of SMCT-1 likewise had no effect.
Conclusions: An *in silico* model of SCFA metabolism has been contructed from sparse parametric data. The model predicts perturbation in extracellular proprtions of propionate and butyrate will affect the acyl-coA:coA-SH ratio. The model has generated testable hypotheses which are now subject to wetlab experimentation. Limitations of the model currently being addressed through iterative testing-experimentation cycles include effect of product as a cofactor in the functional modification of the enzyme pathway, and the lack on metabolic sinks.

1. Astbury SM & Corfe BM (2012) Uptake and metabolism of the short-chain fatty acid butyrate, a critical review of the literature. *Curr Drug Metab* **13**(6), 815–821.