Butyrate induces oxidative metabolism of other mitochondrial substrates in colonocytes

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Butyrate, a short chain fatty acid, is considered important for gut health due to its role as primary energy source for colonocytes. However, high butyrate levels may be detrimental for intestinal cells, because of a limited capacity to oxidize butyrate. As a result, butyrate could accumulate intracellularly and cause damage, possibly via inhibition of histone deacetylases. Since butyrate levels in the colon fluctuate and are driven largely by dietary intake, it is important to understand the fate of butyrate in the colon. We now investigated the metabolic consequences of long and short-term butyrate exposure both in vitro using human and pig cells and in vivo in pigs. In cultured cells (HT29, Caco-2 and HCT-116), acute exposure to butyrate increased oxygen consumption, as has also been observed by other researchers. However, a simultaneous decrease in extracellular acidification was observed, indicating that glycolysis was inhibited. Furthermore, oxygen consumption did not increase in response to butyrate when no glucose was present in the medium. Taken together, these results lead us to believe that butyrate itself was not responsible for the observed oxygen consumption. Instead, butyrate stimulated pyruvate flux towards the mitochondria. Indeed, blocking of the mitochondrial pyruvate carrier likewise inhibited increased oxygen consumption upon butyrate treatment. Long-term exposure to butyrate (72 hours) decreased mitochondrial bioenergetics of high-glucose cultured HT29 cells, while not significantly affecting low-glucose cultured cells. We therefore hypothesize that the observed increased pyruvate flux in high-glucose HT29 may lead to increased reactive oxygen species formation, which leads to decreased mitochondrial function in the long run. Similar to the high-glucose HT29 cells exposed to butyrate for 72h, freshly isolated colon cells from pigs fed a fibre diet also showed a decrease in metabolic function. This indicates that increased butyrate concentrations may also negatively impact metabolic function under physiological conditions.