An Introduction to Butyrate

Key Points
✔ Butyrate is one of the short chain fatty acids
✔ Butyrate is an important element of nutrition for colonocytes
✔ Butyrate contributes to a number of aspects of good health: furthermore, alterations of butyrate are noted in several gut disorders.
✔ The role of butyrate as a therapeutic intervention is now being explored

What is butyrate?
Sodium butyrate, also known as butyric acid, belongs to a group of short chain fatty acids (SCFA) that have important roles in health and in disease.

The SCFA comprise a group of compounds characterised by their size that are predominantly produced following bacterial digestion of dietary starches (non-digestible carbohydrate/fibre). The SCFA, which include butyrate, propionate and acetate, have important local physiological actions. Although butyrate is not present in the greatest quantity, it is thought to have the greatest local effects in the colon. Consequently, this commentary focuses mainly on this SCFA.

Where does butyrate come from?
Although some foods contain butyrate (such as cow’s milk), the main source of butyrate production is the intestinal microbiota themselves. It is increasingly clear that the intestinal microbiota, which comprises more than 10^{13} bacterial organisms, along with fungi, viruses, and other elements, plays a critical role in health (and also in disease). The intestinal microbiota develops early in life, with adult patterns established during the preschool years. These organisms provide numerous key roles for us all: one of these is the production of butyrate and other SCFA.

Certain groups of bacteria normally resident in the gut act to digest dietary fibre and produce butyrate. Consequently, the two key factors associated with luminal production and levels of butyrate are dietary patterns (fibre content) and the intestinal microbiota. Low fibre intake and dysbiosis (disruption of the normal balance of the bacteria) appear to both be linked with reduced production of butyrate and potential consequent adverse effects. In contrast, adequate optimal intake of fibre (especially non-digestible carbohydrates) may enhance butyrate production. Furthermore, optimisation of the intestinal microbiota, and its metabolic activity, should enable optimal butyrate production. Prebiotics and probiotic supplementation may enhance these activities.

Why is butyrate important?
Butyrate contributes directly to colonic health. Butyrate is taken avidly by colonocytes, especially in the right colon, via a specific receptor. Butyrate provides a key source of nutrition and energy for these cells. Butyrate comprises approximately 70% of fuel for colonocytes: the rest is derived from glutamine and glucose.

The intestinal epithelium provides an important barrier limiting movement of antigens or other molecules from the lumen. Altered barrier function occurs in several diseases affecting the gut, such as inflammatory bowel disease and coeliac disease. Butyrate has been shown to directly enhance barrier function by upregulating the production of several proteins integral to the activity of the tight junctions between cells and by modifying the location of other key proteins within epithelial cells.

Butyrate is also shown to upregulate key anti-microbial proteins in the gut, which directly modulate bacterial colonisation. One of these antimicrobial proteins is called cathelicidin: the production of cathelicidin is increased after exposure to butyrate. Butyrate also contributes to ion absorption, visceral perception, motility and oxidative status. Extra-intestinal effects are also demonstrated, but these are less significant than the important homeostatic effects of butyrate in the gut.

What can happen if there is not enough butyrate?
Lack of butyrate is exhibited in several distinct clinical scenarios. Butyrate deficiency is thought to be one of the key reasons for the development of diversion colitis, an entity that may occur when there is no flow through the colon. This lack of flow affects both the delivery of dietary fibre to the colon and the patterns of the colonic flora. Diversion colitis can be prevented or treated by the local administration of butyrate. SCFA can be delivered by enema or into a mucosal fistula directly to the disused section of colon, leading to improvement or complete resolution of inflammatory changes and symptoms.
Suboptimal levels of butyrate consequent to low dietary fibre intake may also be one component of the events that lead to colon cancer. Butyrate is associated with the protection against the development of colorectal carcinoma. Butyrate leads to increased apoptosis (programmed cell death) of cancer-derived cells and also contributes to several other aspects of cell cycling. Together these effects may prevent the progression of changes that ultimately leads to colon cancer. Low levels may therefore, lower the threshold for these changes, giving increased risk of cancer development.

Furthermore, evidence suggests that reduced butyrate is associated with the development of ulcerative colitis (UC), one of the types of inflammatory bowel diseases (IBD). Low levels of butyrate have been demonstrated in colonic biopsies obtained from individuals with active UC. The application of butyrate via enema or in oral formulations, appears to have direct and/or adjunctive anti-inflammatory benefits in this condition. In vitro studies also demonstrate direct anti-inflammatory effects, with for example, reduced production and release of interleukin (IL)-12. Butyrate also modulates the activity of Nuclear-Factor (NF)-xB, a key intracellular signal transduction pathway. Interference with this key signalling pathway leads to a fall in subsequent pro-inflammatory cytokines. Furthermore, animal studies of colitis also demonstrate that the administration of butyrate reduces inflammation via several particular mechanisms.

Reduced butyrate may also contribute to the development of and/or symptoms seen in irritable bowel syndrome (IBS), which is even more common than the other conditions mentioned above. Potential mechanisms leading to this include perturbations of the intestinal microbiota (less butyrate production) and disruption of the normal balance between the gut and the enteric nervous system. Recent studies have shown that butyrate administration leads to a reduction or resolution of gut symptoms (especially in diarrhoea-predominant IBS) and improved quality of life in individuals with known IBS.

Can butyrate be taken therapeutically?

Although experimental work has clearly demonstrated numerous activities of butyrate using various models, such as in vitro cell culture models, the metabolism of butyrate in the gut means that the active agent needs to be delivered to the proximal colon in sufficient quantity to be able to have the desired effects. Oral butyrate that is released more proximally in the gut may limit the amount that actually reaches the colon, the target organ in this case. In addition, butyrate preparations have typically not been able to overcome the unpleasant taste and odour of butyrate.

A microgranular sustained release formulation of butyrate that delivers the active agent into the distal intestinal tract would overcome the issue of metabolism in the gut and avoid the taste or smell issues. Such a preparation would open the door to further applications for butyrate as a therapeutic intervention.

Conclusions

Butyrate is a key fatty acid that contributes to the health of our bowel. Altered production, for various reasons, is associated with a number of important, chronic conditions involving the gut. Dietary patterns and dysbiosis of the colon microbiota may contribute together to reductions in butyrate levels. The provision of butyrate as a specific therapy has been highlighted with the development and availability of an oral butyrate preparation that is able to reach the colon. The administration of butyrate may contribute positively to the well-being of individuals with various gut disorders.

Bibliography and Further reading