

# Butyrate Reference Pages

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## **Butyrate induces cell apoptosis through activation of JNK MAP kinase pathway in human colon cancer RKO cells.**

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### **Abstract**

Butyrate has been shown to display anti-cancer activity through the induction of apoptosis in various cancer cells. However, the underlying mechanism involved in butyrate-induced apoptosis is still not fully understood. Here, we investigated the cytotoxicity mechanism of butyrate in human colon cancer RKO cells. The results showed that butyrate induced a strong growth inhibitory effect against RKO cells. Butyrate also effectively induced apoptosis in RKO cells, which was characterized by DNA fragmentation, nuclear staining of DAPI, and the activation of caspase-9 and caspase-3. The expression of anti-apoptotic protein Bcl-2 decreased, whereas the apoptotic protein Bax increased in a dose-dependent manner during butyrate-induced apoptosis. Moreover, treatment of RKO cells with butyrate induced a sustained activation of the phosphorylation of c-jun N-terminal kinase (JNK) in a dose- and time-dependent manner, and the pharmacological inhibition of JNK MAPK by SP600125 significantly abolished the butyrate-induced apoptosis in RKO cells. These results suggest that butyrate acts on RKO cells via the JNK but not the p38 pathway. Butyrate triggered the caspase apoptotic pathway, indicated by an enhanced Bax-to-Bcl-2 expression ratio and caspase cascade reaction, which was blocked by SP600125. Taken together, our data indicate that butyrate induces apoptosis through JNK MAPK activation in colon cancer RKO cells.

## **Role of butyric acid and its derivatives in the treatment of colorectal cancer and hemoglobinopathies**

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### **Abstract**

Butyric acid, a short chain fatty acid (SCFA), is a natural component of the animal metabolism. Physiological concentrations induce multiple and reversible biological effects. They concern regulatory mechanisms of gene expression conducing to promote markers of cell differentiation, apoptosis and cell growth control. The described hyperacetylation of histones and the induction of several immune or non-immune cell-activating mediators are consistent with the pleiotropic stimulatory effect of the agent. Butyric acid is considered as a biological response modifier (BRM) and is an interesting tool for biological studies. The history of butyric acid as a putative medication in human health is spanning since 60 years and is confusing in part because of conflicting data between exciting experimental results and clinical trials. In light of minimal impact of systemic therapy and the short half-life of the saline molecule used, it is evident that continuous infusions of butyrate are required to improve the efficacy of the treatment. Butyric acid has been viewed with skepticism because of less convenient for long-term chronic therapy. New experimental data from several studies conduced within the past decade with butyric derivatives, delivery systems, and long-acting prod-rugs, have demonstrated the practical value of the therapeutic concept. To support issues regarding clinical development, it was of interest to evaluate the recent information, showing butyric acid currently considered as therapeutic purposes in the treatment of colorectal cancer and hemoglobinopathies.

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## **Short-chain fatty acid in the human colon. Relation to inflammatory bowel diseases and colon cancer.**

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### **Abstract**

Short chain fatty acids (SCFAs) are the end products of anaerobic bacteria break down of carbohydrates in the large bowel. This process, namely fermentation, is an important function of the large bowel; SCFAs, mainly acetate, propionate and butyrate account for approximately 80% of the colonic anion concentration and are produced in nearly constant molar ratio 60:25:15. Among their various properties, SCFAs are readily absorbed by intestinal mucosa, are relatively high in caloric content, are metabolized by colonocytes and hepatocytes, stimulate sodium and water absorption in the colon and are trophic to the intestinal mucosa. While the fermentative production of SCFAs has been acknowledged as a principal mechanism of intestinal digestion in ruminants, the interest in the effects of SCFAs production on the human organism has been raising in the last ten years. SCFAs are of major importance in understanding the physiological function of dietary fibers and their possible role in intestinal neoplasia. SCFAs production and absorption are closely related to the nourishment of colonic mucosa, its production from dietary carbohydrates is a mechanism whereby considerable amounts of calories can be produced in short-bowel patients with remaining colonic function and kept on an appropriate dietary regimen. SCFAs enemas or oral probiotics are a new and promising treatment for ulcerative colitis. The effects have been attributed to the oxidation of SCFAs in the colonocytes and to the ability of butyrate to induce enzymes (i.e. transglutaminase) promoting mucosal restitution. Evidence is mounting regarding the effects of butyrate on various cell functions the significance of which needs further considerations. Up until now, attention has been related especially to cancer prophylaxis and treatment. This article briefly reviews the role of SCFAs, particularly butyrate, in intestinal mucosal growth and potential clinical applications in inflammatory and neoplastic processes of the large bowel.

## Butyrate inhibits inflammatory responses through NF $\kappa$ B inhibition: implications for Crohn's disease

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### Abstract

**BACKGROUND/AIM** Proinflammatory cytokines are key factors in the pathogenesis of Crohn's disease (CD). Activation of nuclear factor kappa B (NF $\kappa$ B), which is involved in their gene transcription, is increased in the intestinal mucosa of CD patients. As butyrate enemas may be beneficial in treating colonic inflammation, we investigated if butyrate promotes this effect by acting on proinflammatory cytokine expression.

**METHODS** Intestinal biopsy specimens, isolated lamina propria cells (LPMC), and peripheral blood mononuclear cells (PBMC) were cultured with or without butyrate for assessment of secretion of tumour necrosis factor (TNF) and mRNA levels. NF $\kappa$ B p65 activation was determined by immunofluorescence and gene reporter experiments. Levels of NF $\kappa$ B inhibitory protein (I $\kappa$ B $\alpha$ ) were analysed by western blotting. The in vivo efficacy of butyrate was assessed in rats with trinitrobenzene sulphonic acid (TNBS) induced colitis.

**RESULTS** Butyrate decreased TNF production and proinflammatory cytokine mRNA expression by intestinal biopsies and LPMC from CD patients. Butyrate abolished lipopolysaccharide (LPS) induced expression of cytokines by PBMC and transmigration of NF $\kappa$ B from the cytoplasm to the nucleus. LPS induced NF $\kappa$ B transcriptional activity was decreased by butyrate while I $\kappa$ B $\alpha$  levels were stable. Butyrate treatment also improved TNBS induced colitis.

**CONCLUSIONS** Butyrate decreases proinflammatory cytokine expression via inhibition of NF $\kappa$ B activation and I $\kappa$ B $\alpha$  degradation. These anti-inflammatory properties provide a rationale for assessing butyrate in the treatment of C

# Oral butyrate for mildly to moderately active Crohn's disease

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## Summary

**BACKGROUND:** Butyrate exerts anti-inflammatory effects in experimental colitis and on Crohn's disease lamina propria mononuclear cells in vitro.

**AIM:** To explore the efficacy and safety of oral butyrate in Crohn's disease.

**METHODS:** Thirteen patients with mild–moderate ileocolonic Crohn's disease received 4 g/day butyrate as enteric-coated tablets for 8 weeks. Full colonoscopy and ileoscopy were performed before and after treatment. Endoscopical and histological score, laboratory data, Crohn's disease activity index and mucosal interleukin (IL)-1 $\alpha$ , IL-6, IL-12, interferon- $\alpha$ , tumour necrosis factor- $\alpha$  and nuclear factor-kappa B (NF- $\kappa$ B) were assessed before and after treatment.

**RESULTS:** One patient withdrew from the study, and three patients did not experience clinical improvement. Among the nine patients (69%) who responded to treatment, seven (53%) achieved remission and two had a partial response. Endoscopical and histological score significantly improved after treatment at ileocaecal level ( $P < 0.05$ ). Leucocyte blood count, erythrocyte sedimentation rate and mucosal levels of NF- $\kappa$ B and IL-1 $\alpha$  significantly decreased after treatment ( $P < 0.05$ ).

**CONCLUSIONS:** Oral butyrate is safe and well tolerated, and may be effective in inducing clinical improvement/remission in Crohn's disease. These data indicate the need for a large investigation to extend the present findings, and suggest that butyrate may exert its action through downregulation of NF- $\kappa$ B and IL-1 $\alpha$ .