

N-(1-carbamoyl-2-phenyl-ethyl) butyramide, a new synthetic butyrate derivative, reduces intestinal inflammation in dextran sodium sulphate-induced colitis.

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Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease, whose etiology is currently unknown. Although several studies have shown the benefits of butyrate enemas in UC, studies using the oral route are rare in the literature because of its low palatability and stability that limit a wide therapeutic use of this substance (Berni Canani et al., 2011). We have recently obtained a high palatable synthetic butyrate derivative, N-(1-carbamoyl-2-phenylethyl) butyramide (FBA). FBA is present in a solid, poorly hygroscopic, easily weighable form, stable to acids and alkalis and capable of releasing butyric acid at small and large bowel level in a constant manner over time. This product has demonstrated a toxicological profile comparable to that of butyrate. In this study we comparatively evaluated the effects of this new compound and of the equimolecular dose of sodium butyrate (Butyrate) in dextran sulfate sodium (DSS)-induced colitis.

Experimental colitis was induced in male BALB/c mice by 2.5% DSS in drinking water for 5 days. The oral treatment with Butyrate (20 mg/kg/d) or FBA (42.5 mg/kg/d), started 7 days before DSS challenge and continued for all experimental period (20 days). Analysis of disease activity index (DAI), histological assessment, colonic mucosa integrity, inflammatory markers, oxidative stress and neutrophil infiltration was performed for both therapeutic treatments.

DSS induced a significant decrease in animal weight, and a reduction of intestinal and colonic length. Morphological analysis of colonic tissue by hematoxylin and eosin staining revealed that in DSS-treated mice the crypts and the normal architecture of the mucosa were lost. The inflammatory status of the mucosa in DSS animals was assessed by the increase in pro-inflammatory enzymes (COX-2 and iNOS) and cytokines (TNF- α and IL-6). Moreover, DSS increased neutrophil infiltration (myeloperoxidase determination) and reduced occludin and IL-10 mRNA levels in the colonic mucosa accompanied with a significant serum adiponectin reduction. Butyrate and FBA showed marked and protective effects on weight loss, oxidative damage and structural integrity of colonic mucosa. In addition both Butyrate, and in particular FBA, were able to significantly limit mucosal inflammation, decreasing COX-2, iNOS and pro-inflammatory cytokines. A similar effect potency was observed on reducing myeloperoxidase and partially restoring adiponectin and IL-10 levels.

Our results show a protective effect of Butyrate to limit early molecular events underlying inflammatory process linked to intestinal damage, suggesting its potential clinical utility as preventive and therapeutic strategy for UC. Since FBA does not have the characteristic odor of rancid cheese, this derivative may represent a viable therapeutic alternative to Butyrate, favoring a better compliance and a greater effectiveness.

Berni Canani R, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World J Gastroenterol.* 2011;17:1519-28