Role of sodium butyrate and of its new prodrug N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA) in gastrointestinal transit, castor oil-induced diarrhoea, and croton oil-induced intestinal inflammation

R. Russo[1] , C. De Caro[1], C.Avagliano[1], C. Cristiano[1,2], N.S.Orefice[1], G. D'Agostino[1], G. LaRana[1], G. Mattace Raso [1], R. Berni Canani [3], R. Meli[1], A. Calignano[1].

[1]Dept. of Pharmacy, University of Naples Federico II, Naples, Italy
[2] Drug Discovery and Development, Istituto Italiano di Tecnologia, via Morego 30, Genova, Italy
[3] Dept. of Translational Medicine–Pediatric Section and European Laboratory for the Investigation of Food Induced Diseases, University of Naples 'Federico II', 80131 Naples, Italy

Among the main luminal factors endogenously produced in the colon and known to modulate gut functions are short chain fatty acids. They are generated in the large intestine as a result of bacterial fermentation of dietary fibres and resistant starch is considered the main source of butyrate has an important role in regulating colonic mucosa homeostasis (1). In particular, butyrate is the primary energy source for the colonic epithelium, it has trophic effects, and reduces oxidative stress by increasing glutathione concentrations and is involved in electrolytes resumption (2). Several studies have shown that butyrate has anti-carcinogenic and anti-inflammatory effects (3). *In vitro*, butyrate has been shown to reduce inflammation by inhibition of NFκB activation (4) and up-regulation of PPARγ (5). *In vivo*, several studies have demonstrated a decrease in inflammation due to rectal administration of butyrate or mixtures of SCFA in patients with active ulcerative colitis (6,7) and diversion colitis, (8,9) although not all studies were able to show significant effects (9).We have tested the effects of a synthetic butyrate derivative able to release butyrate at intestinal level in comparison to equimolecular doses of sodium butyrate (BuNa) in intestinal mice transit, and in castor oil-induced diarrhoea. Sodium butyrate (10-100 mg/kg) and N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA) (21,2-212 mg/kg) have been orally administered 30 min before the charcoal meal. Thirty minutes after the mice were sacrificed and the length travelled by the charcoal meal measured. Both acute or repeated treatment of BuNa or FBA were equally able to reduce in a dose dependent manner the length travelled by the charcoal meal. In castor oil–induced diarrhoea, in acute treatment only the high dose of both BuNa and FBA reduced numbers of evacuations; while, repeated treatment of FBA resulted more effective than equimolecular doses of BuNa. Similar results have also been obtained in croton oil-induced intestinal inflammation. In summer, our results indicate that in the regular peristalsis BuNa and FBA are equally active, whereas the local intraluminal release of butyrate, due to FBA, is a key point to obtain a strong effect in controlling non physiological peristalsis. We conclude that during pathological states in which luminal secretion is increased, the intraluminal release of butyrate plays an important role in controlling secretion, and diarrhoea.

References

1. S Macfarlane et al., Proc Nutr Soc (2003); 62:67-72
2. HM Hamer et al., Clin Nutr. (2009); 28(1):88-93.
3. H.M. Hamer, Aliment Pharmacol Ther **27** (2008), pp. 104–119.
4. J.P. Segain, et al., Gut **47** (2000), pp. 397–403.
5. M. Kinoshita, et al., Biochem Biophys Res Commun **293** (2002), pp. 827–831.
6. H. Luhrs, et al., Scand J Gastroenterol **37** (2002), pp. 458–466.
7. W. Scheppach, Gastroenterology **103** (1992), pp. 51–56.
8. J.M. Harig,et al., N Engl J Med **320** (1989), pp. 23–28.
9. F. Guillemot, Dis Colon Rectum **34** (1991), pp. 861–864.