Analgesic properties of N-(1-carbamoyl-2-phenyl-ethyl) butyramide a new synthetic butyrate prodrug in a model of acute and visceral pain.

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Short chain fatty acids (SCFAs) are derived from microbial fermentation of undigested dietary fibres in the colon (1). The amount of SCFAs (mainly acetate, propionate and butyrate) are produced in the colon and butyrate is known to modulate numerous processes (2). Previously, positive effects of butyrate on inflammation in active distal ulcerative colitis have been reported as well as the ameliorative effects on several inflammatory parameters such as cytokine production and myeloperoxidase activity, primarily via inhibition of nuclear factor kappa B activation (3,4). We have tested the effects of sodium butyrate (10-100 mg/kg) and of a synthetic butyrate derivative (with good stability and solubility, absence of smell and taste) N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA) at equimolecular doses (21,2-212 mg/kg) in a models of visceral pain (acetic acid-induced writhing. In acute experiments, sodium butyrate and FBA at all the doses tested, were ineffective in acetic acid-induced writhing. While, repeated treatments (once a day for four days) both drugs, resulted active in reducing the number of writhings; in particular our derivate resulted much active than sodium butyrate. Using PPAR-gamma antagonist (GW9662, 1mg/kg; ip) and wild-type (WT) and PPAR-alpha knock-out (KO) C57BL6 mice, we have investigated the role of these receptors in sodium butyrate or FBA-induced analgesia. Results showed that PPAR-gamma, rather than PPAR-alpha, was mainly involved. Finally, western blot experiments on colon confirmed these data. In summary, our data indicate that single administration of sodium butyrate or FBA are non effective, whereas the increase of plasmatic levels of butyrate due to repeated treatment, is necessary for modulation of visceral pain.

References

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