Analgesic effects of sodium butyrate and phenylalanine-butyramide derivative in acute and chronic pain models

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Butyrate is a natural short-chain fatty acid (SCFA) present in dairy products and produced by commensal anaerobic fermentation of undigested carbohydrates in the colon [1]. Clinical trials suggest that butyrate exerts its anti-inflammatory properties in human inflammatory bowel disease, including ulcerative colitis, proctosigmoiditis and chronic radiation proctitis [2-5]. Conversely, preclinical studies, performed in rats, showed that butyrate enemas prolong visceral hyperalgesia following trinitro-benzene sulfonic acid-induced colonic inflammation [6]. While local application of butyrate on distal colonic mucosa has been evaluated with discordant results [7-9], its beneficial effect after systemic administration on pain perception appears more clear, but little investigated. Recently, Kukkar [10] showed that oral administration of butyrate attenuates neuropathic pain symptoms in a chronic constriction injury (CCI) model, which may be mainly attributed to its ability to decrease the release of pro-inflammatory mediators during neuropathy development. In the present study we investigated the role of sodium butyrate (butyrate), and its more palatable derivative, the N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA), in animal models of acute and chronic pain. We found that oral administrations of butyrate (10-200 mg/Kg) or equimolecular FBA (21.2-424 mg/Kg) reduced visceral pain in a dose- and time-dependent manner. Both drugs were also effective in the formalin test, showing a rapid antinociceptive effect. This analgesic effect was blocked by glibenclamide, suggesting the involvement of ATP-dependent K^+ channels. Moreover, following repeated administration, butyrate(100-200 mg/Kg) and FBA (212-424 mg/Kg) retained their analgesic properties in a model of neuropathic pain, reducing mechanical and thermal hyperalgesia in the chronic constriction injury (CCI) model. The involvement of peroxisome proliferator-activated receptor (PPAR)-α and -γ for the analgesic effect of butyrate was also investigated by using PPAR-alpha null mice or the PPAR-gamma antagonist GW9662. Western blot analysis confirmed the role of peroxisome receptors in butyrate effects, thus evidencing the increase of PPAR-α and -γ expression, associated to the reduction of inflammatory markers (COX-2, iNOS and TNF-α). In conclusion, we describe the role of butyrate-based drugs in pain, identifying different and converging non-genomic and genomic mechanisms of action, which cooperate in nociception maintenance.

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