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Colonic Butyrate- algesic or analgesic?

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Abstract

Irritable bowel syndrome (IBS) is a common health issue that is characterized by abdominal pain, abnormal bowel movements and altered visceral perception. The complexity and variability in symptoms pose serious challenges in treating IBS. Current therapy for IBS is primarily focused on reducing the abdominal pain, thereby improving the quality of life to a significant extent. Although the use of fiber rich diet is widely recommended in treating IBS, some studies have questioned its use. Intracolonic butyrate, a short chain fatty acid, is primarily produced by the fermentation of dietary fibers in the colon. In the existing literature there are conflicting reports about the function of butyrate. In rats it is known to induce visceral hypersensitivity without altered pathology, whereas in humans it has been reported to reduce visceral pain. Understanding the molecular mechanisms responsible for this contrasting effect of butyrate is important before recommending fiber rich diet to IBS patients.

Keywords

Inflammatory bowel syndrome; *colonic hypersensitivity*; *short chain fatty acids*; *sodium butyrate*

Introduction

Irritable bowel syndrome (IBS), a chronic debilitating gastrointestinal disorder with no identifiable organic abnormalities or a convincing pathophysiology affects about 10-15% of the population worldwide.[1] IBS is characterized by abdominal pain or discomfort associated with altered bowel habits and often accompanied by sensations of bloating, urgency or incomplete evacuation.[2] Although the underlying mechanism that results in IBS remains poorly understood, it is generally accepted that dysfunction at the brain–gut axis, with alterations in the components of central and peripheral nervous system and social stress contribute to this disorder.[3] One of the classical symptoms of IBS is increased sensitivity to visceral stimuli.[4] Studies have shown that about 20%-90% of IBS patients are viscerally hypersensitive and this is currently considered to be the key clinical symptom in these patients.[5] The complexity and diversity of IBS symptoms make its treatment strategy quite challenging. Currently, the main objective of the treatment of IBS is focused on the relief of abdominal pain and then treating for improving bowel disturbances. Traditional symptom-based therapies have been found to be ineffective in the treatment of IBS and do not modify the natural history of the disorder. The use of prebiotics or probiotics in the treatment for IBS has become increasingly popular as an alternative to pharmacological interventions. In

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addition, changes in dietary habits such as increasing fiber intake are widely recommended for the management of IBS symptoms. Soluble fibers are more effective than insoluble fibers in alleviating global symptoms and relieving constipation, although fiber in general has only a marginal benefit in treatment of overall IBS symptoms.[6]

The colon is inhabited by different populations of micro-organisms where a true symbiosis with the host exists for well-being and health.[7] Fermentation of undigested and unabsorbed carbohydrates, such as resistant starches and dietary fibers by the colonic bacterial flora within the intestinal lumen produces short-chain fatty acids (SCFAs) like acetate, propionate and butyrate, which are utilized by the colonic mucosa.[8] The amount of these SCFAs produced in the colon depends on the site of fermentation, the diet composition, gut transit time and the composition of the colonic microbial flora. While propionate is largely taken up by the liver, acetate enters the systemic circulation to be metabolized by the peripheral tissues. Butyrate on the other hand functions as the major energy source for colonocytes and is reported to modulate several cellular processes.[9] Several studies have shown an inverse relationship between dietary fiber intake and the incidence of colorectal cancer, although epidemiological studies are still inconclusive.[10,11,12] It has been hypothesized that increased colonic concentrations of butyrate might be responsible for the observed protection offered by high fiber diets.[13] This beneficial effect of butyrate coupled with the rather low consumption of fermentable dietary fiber in today's Western diet, has prompted the food manufacturers' to supplement dietary fibers in their food and beverages so as to increase the colonic butyrate concentrations by slow bacterial fermentation.[14] Butyrate has been shown to act as a signal metabolite affecting epithelial cell proliferation, apoptosis and differentiation.[15] There is sufficient evidence that butyrate beneficially affects several inflammatory parameters such as cytokines and myeloperoxidase activity, primarily via inhibition of nuclear factor kappa B activation.[16] Furthermore, butyrate stimulates intestinal mucus production, thereby supporting the mucosal barrier function,[17,18] increases anti-oxidant capacity,[19,20] increases mucosal blood flow[21] and decreases colonic epithelial permeability.[22,23] Butyrate has also been shown to increase in vitro crypt proliferation,[24] reduce inflammation in patients with diversion colitis,[25] and reduce diarrhea.[26] It has been suggested that butyrate plays a major role in mucosal repair,[27] inflammation-related repairs in humans and is also reported to offer protection against colonic carcinogenesis in rats.[28,29,30] These findings have prompted the effective use of butyrate enemas in treating patients with bowel diseases such as distal ulcerative colitis.[31,32] Sodium butyrate enema has been used in the treatment of inflammatory bowel disease (IBD) and reported to offer a beneficial effect both in vivo and in vitro.[22,33] The mechanism of topical treatment of sodium butyrate may relate to its nutritional effect, which has shown to provide the energy source for colonic epithelium cells, accelerate aerobic metabolism of SCFAs and regulate epithelium cell proliferation.[34] In spite of experimental studies having shown a positive role for butyrate in the colon, complete comprehensive clinical studies on healthy and IBS patients are still inconclusive.

Controversy of butyrate in visceral pain

Although several investigators have reported on beneficial effects of butyrate in the colon, studies carried out by Bourdu et al[35] showed that butyrate might indeed be involved in causing colonic hypersensitivity. Butyrate enemas for 3 days to Sprague-Dawley rats resulted in a sustained, dose-dependent decrease in their pain threshold level, leading to colonic hyperalgesia and to a lesser extent a referred cutaneous mechanical hyperalgesia, particularly in female rats with no macroscopic and histologic modifications of the colonic mucosa. The observed condition exactly mimics the clinical condition seen in patients with IBS and therefore it has been suggested for using this as a model of non-inflammatory chronic colonic hypersensitivity. Over the years several investigators have used this model

of so-called IBS for their studies and have raised questions about the therapeutic benefit of dietary fibers or butyrate in patients with IBS.[36, 37]

Interestingly, studies carried out by Vanhoutvin et al[38] show a different picture on the role of butyrate in the human colon. Intraluminal administration of a physiologically relevant dose (50 and 100 mmol/L) of butyrate into the distal colon increases compliance and decreases pain and discomfort in healthy human subjects. This result indicates significant decrease in visceral perception, which is in sharp contrast to the findings from rat studies, in which butyrate prolonged visceral hyperalgesia in trinitro-benzene sulfonic acid (TNBS)-induced colonic inflammation in rats[39] and also induced visceral hypersensitivity in control animals.[35] In spite of the study being performed only on healthy human subject and not on IBS patients, the authors conclude that butyrate produces a remarkable improvement in the parameters of visceral perception and suggest a possible beneficial effect of butyrate in disorders, which are associated with visceral pain.

While animal studies question the use of butyrate in treating IBS, the human studies advocates the use of butyrate in reducing colonic pain. Although both the studies have reported on the possible mechanism of action of butyrate in producing the their observed effects, it is important to understand how and why butyrate acts differentially in animals and humans, in spite of being normally present in the colon.

Possible underlying mechanism of butyrate in pain mechanism

In rats

As indicated in the previous section, butyrate enemas resulted in a sustained, dose-dependent decrease in the pain threshold level, leading to colonic hypersensitivity along with a referred cutaneous mechanical hyperalgesia.[35] The preliminary studies performed to elucidate the mechanism involved in hypersensitivity suggest the involvement of peptidergic (i.e., substance P and CGRP containing) C-fibers. This is evidenced from the observation that butyrate enemas produced significantly less colonic pain and referred somatic hyperalgesia in neonatally capsaicin-treated rats compared to vehicle treated controls.[35] There is ample evidence to show that neonatal treatment with capsaicin results in a selective elimination of C-fiber nociceptive afferents that express transient receptor potential vanilloid one (TRPV1) ion channels.[40] The study also suggests a possible involvement of calcitonin gene-related peptide (CGRP) receptors because of an observed reduction in the butyrate-induced hypersensitivity following administration of CGRP antagonist $CGRP_{8\text{-}37}$. In addition, the authors also report the involvement of opiodergic system in this model as mu-opioid receptor agonist morphine and kappa-opioid receptor agonist U50,488H were effective in reducing colonic hypersensitivity.[35] Although butyrate is formed in the colon, the dose used in this study (200mM) is much higher than that is found in the colon under normal circumstances. This might be a contributing factor in the observed visceral hypersensitivity.

Recently, Matricon et al[41] reported on the involvement of spinal cord plasticity and acid-sensing ion channels 1A (ASIC1A) in a rodent model of non-inflammatory colonic hypersensitivity. Treatment with butyrate was found to upregulate ASIC1A in the lumbar spinal cord, causing spinal sensitization and this might be responsible for the observed colonic hypersensitivity in this model. This was confirmed by preventing the colonic hypersensitivity following intrathecal administration of PcTx1, a specific ASIC1A antagonist.

In Humans

Although no biopsy samples were taken to study the molecular mechanism following butyrate enemas, three possible mechanisms have been proposed by which butyrate might have caused a decrease in colonic pain in human subjects [38] – (1) the decrease in visceral perception due to butyrate treatment could be due to direct modulation of 5-hydroxytryptamine (5-HT or serotonin) release, which can increase the compliance of the hollow viscera leading to decrease in perception, (2) activation of transient receptor potential vanilloid 1 (TRPV1) receptors in the colonic mucosa by butyrate which in turn may indirectly lead to 5-HT release in the gut to alter the perception, (3) overstimulation (i.e., high concentration of butyrate) or repetitive stimulation (i.e., multiple application) of TRPV1 receptors can cause rapid deactivation of the channel due to excessive influx of Ca^{++}. Therefore butyrate may desensitize sensory neurons expressing TRPV1 receptors following repeated administration and (4) butyrate could attenuate visceral perception via inhibition of histone deacetylase (HDAC). In normal biological system, histone acetylases, acetylate the lysine residues of the core histones leading to a less compact and more transcriptionally active chromatin and on the converse, histone deacetylases (HDAC) remove the acetyl groups from the lysine residues leading to the formation of a condensed and transcriptionally silenced chromatin. Inhibition of HDAC results in hyperacetylation of histones thereby inhibiting gene expression. A number of structurally diverse HDAC inhibitors have shown potent antitumor efficacy with little toxicity in in vivo animal studies. Inhibitors like valproate, butyrate and trichostatin A, have previously been reported to induce microglial apoptosis and to reduce inflammation-induced neurotoxicity in rat tissue, which may affect visceral perception.[42]

It is well known that butyrate has diverse effects on cell proliferation, apoptosis and differentiation. Several studies have reported contrary results with respect to the effect of butyrate on colon cancer. This lack of agreement particularly between *in vivo* and *in vitro* studies has been termed the “butyrate paradox”.[43] A number of reasons for this variation in the effects of butyrate have been suggested, like the differences between the *in vitro* and *in vivo* environments, the timing of butyrate administration, the amount of butyrate administered, the source of butyrate and interaction with dietary fat. Considering the above factors, it is possible that butyrate might also function differently in the colon of rats and humans in producing and inhibiting visceral hypersensitivity, respectively. Some of the probable factors could be the (1) concentration of butyrate used in the studies, (2) composition of intestinal microflora and (3) differential metabolism profile of butyrate between rodents and humans. Therefore, the results of animal experiments may not always correlate with the human studies and warrants further investigation to understand the mechanism of action of butyrate. It is our observation from these reports that the dose of butyrate administered plays a critical role in producing the observed effect and hence it is important to know the threshold level of colonic butyrate beyond which it produces hypersensitivity in rats. On the other hand, the results of human experiments necessitates further exploration to know the effect of rectal instillation of butyrate on IBS patients and whether it has any role in modulating visceral pain, since the existing clinical study is restricted only to healthy human volunteer. It has been reported that low amounts of butyrate stimulates cell proliferation while on the contrary high amounts may inhibit it.[44] Considering this report it is possible that butyrate at physiologically relevant concentrations might be effective in decreasing the colonic hypersensitivity whereas a higher concentration might produce an opposite effect. Further studies in this direction are required to obtain conclusive evidence before undertaking clinical trials for the treatment of visceral pain in IBS patients.

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