TOPICAL REVIEW

Short chain fatty acids and colonic health

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Abstract

Recently, colonic health has been linked to the maintaining overall health status and reducing the risk of diseases by changes in lifestyle. Functional foods, such as "prebiotics" and "probiotics", dietary fibers, and other dietary components that target the colon and affect its environment enhancing short fatty acid (SCFA) production have been at the forefront. The topic of this review is the key end products of colonic fermentation, the SCFA butyric, acetic, and propionic acids. SCFA are readily absorbed. Butyrate is the major energy source for colonocytes. Propionate is largely taken up by the liver. Acetate enters the peripheral circulation to be metabolized by peripheral tissues. Specific SCFA may reduce the risk of developing gastrointestinal disorders, cancer, and cardiovascular disesase *(Fig. 1, Ref. 30)*. Full Text (Free, PDF) *www.bmj.sk*.

Key words: colon cancer, life style, nutrition, short chain fatty acids.

Colorectal cancer (CRC) is the fourth most common cause of cancer-related mortality in the world. Within the Europe, North America, Australia and New Zealand, it is the second most common cancer after lung or breast and in general, the incidence and mortality of the disease are increasing (Boyle and Langman, 2000).

CRC is more common in some families and in certain conditions like ulcerative colitis, history of polyps, or in women with the history of ovarian or uterine cancer. Many factors have been found to be associated with CRC, such as low levels of physical activity, smoking, alcohol consumption, high body weight, history of the colon or rectum polyps, low intake of fruits and vegetables and high meat consumption. Evidence suggests that diet plays a significant role in the aetiology of CRC (Gill and Rowland, 2002). To establish a causal relationship between the diet and CRC risk and to identify the dietary components involved, human intervention trials are required. These studies will be crucial to the success of dietary recommendations to maximize prevention of colonic disease.

Biomarkers for colorectal cancer

The issue with the human intervention studies is that cancer is not a practical endpoint in terms of numbers, cost, study duration and ethical considerations. Particularly, the long lag phase (up to 20 years) between exposure to a carcinogenic event and appearance of tumours is a problem. An alternative strategy is the use of intermediate endpoint biomarkers of cancer, which may be biochemical, molecular, cellular or rooted in pathologic change (e.g. recurrence of polyps, faecal water, epithelial markers). Biomarkers have been developed from an understanding of the sequence of events leading to colonic cancer, the biology of normal mucosa and the factors associated with changes symptomatic of progression toward cancer and the manifestation of cancer. The advantages of biomarkers are that they represent short-term/intermediate endpoint, which allow intervention in a reasonable time. Ethical approval is readily obtainable for biomarker studies as they are minimally invasive, with measurements occuring on an accessible material (faeces and small biopsies, familial adenomatous polyposis). The ideal biomarkers should be sensitive, reproducible and rigorously validated, although this is not the case of all biomarkers in the cancer field. Biomarkers should be causally linked, or correlated with the cancer and hence of a biological significance. Thus validation of

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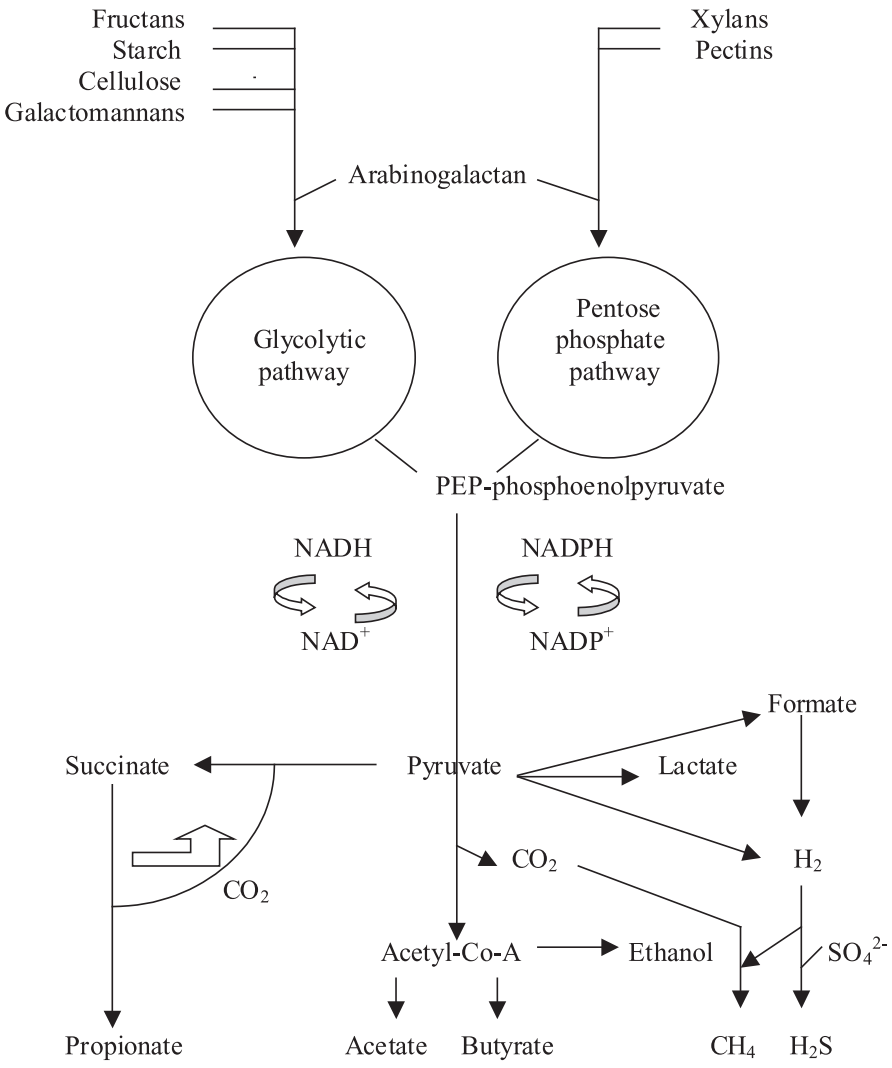

Fig. 1. SCFA production in the colon.
The basic pathway for production of a variety SCFA metabolites by bacterial fermentation in the colonic lumen. (Macfarlane and Gibson, 1996).

a biomarker is critical to its application as a research tool, as an appropriate response from the marker is required when assayed in cancer patients or in healthy individuals on low-risk and high-risk diets for CRC. The biomarkers available for the study of CRC are composed of two main types: – tissue, and – biochemical. Both categories possess distinct advantages.

Tissue biomarkers are analysed from a tissue biopsy and as such necessitate invasive procedures of varying complexities to retrieve samples of rectal/colonic mucosa. The use of biopsies increases the technical complexity of the studies, but reduces the degree of inference required to interpret the results when compared to biochemical markers. Therefore, tissue biomarkers provide the scope to examine a range of cellular aspects intimately linked to CRC.

Biochemical markers, in contrast to the invasive techniques, can be readily measured in blood, urine or faeces, and thus are minimally or non invasive. Biochemical markers are composed of two main groups, mammalian enzymes and gut microflora associated biomarkers. The former are measures of specific endogenous enzyme activity in blood, urine or biopsy specimens, e.g. hepatic enzyme CYP1A2, glutathione S-transferase, whilst the latter include bacterial enzyme activities, faecal metabolites, and short chain fatty acids.

Short chain fatty acids (SCFAs)

The concept of colonic health has become a target for the development of functional foods such as “probiotics, prebiotics, and synbiotics” and other dietary components that target the colon and affect its environment, composition of the microflora, as well as the physiology of the colon, and display distinct health benefits (Bomba et al, 2002). Dietary carbohydrates escaping

digestion/absorption in the small bowel and prebiotics undergo fermentation in the colon and enhancing short chain fatty acids (SCFAs) production. These have been associated with reduced risk of some diseases, including the irritable bowel syndrome, inflammatory bowel disease, cardiovascular disease, and cancer (Roediger,1980; Jenkins et al, 1999; Floch and Hong-Curtiss, 2002).

SCFAs are organic fatty acids with 1 to 6 carbon atoms and are the principal anions which arise from bacterial fermentation of polysaccharide, oligosaccharide, proteins, peptide, and glycoprotein precursors in the colon (Miller and Wolin, 1979; Cummings and Macfarlane, 1991). Fermentation involves a variety of reactions and metabolic processes in the anaerobic microbial breakdown of organic matter, yielding metabolizable energy for microbial growth and maintenance and other metabolic end products for host use. The chief end products are SCFAs together with gases (CO_2, CH_4, and H_2) and heat (Topping and Clifton, 2001). Various population data show that SCFA production is in order of acetate > propionate > butyrate in a molar ratio of approximately 60:20:20 or 3:1:1, respectively in the proximal and distal colon (Cummings, 1981; Cummings et al, 1987; Topping and Clifton, 2001).

Carbohydrates are fermented (Fig. 1) by saccharolytic bacteria primarily in the proximal colon producing linear SCFAs, CO_2 and H_2 (Macfarlane and Macfarlane, 2003), and both the presence of carbohydrates in the colon and their fermentation can alter the colonic physiology. Fermentation of proteins and amino acids by proteolytic bacteria yield branched SCFAs, CO_2, CH_4, H_2, phenols, and amines (Roberfroid, 2005). The primary effect of SCFAs on colonic function is the result of their uptake and metabolism by colocytes, although SCFAs are also metabolic substrates for other host tissues. The production of SCFAs is determined by many factors, including the numbers and types of microflory present in the colon (Roberfroid, 2005), substrate source (Cook and Sellin, 1998), and gut transit time. A large microflora population is present in the human colon at 10^{10} to 10^{11} cfu/g wet wt (Hill, 1995), and more than 50 genera and over 400 species of bacteria have been identified in human feces. Bacterial numbers, fermentation, and proliferation are highest in the proximal colon where substrate – carbohydrate availability is the greatest. Therefore, the principal site of colonic fermentation is the cecum and proximal colon, whereas the distal colon is carbohydrate and water depleted. Specific species such as Bifidobacterium and Lactobacillus have been associated with an improved health, resulting in the emergence of the probiotics, or delivery of specific bacteria to the colon and prebiotics, or the administration of dietary component that promote the growth of specific bacteria with defined metabolic functions. SCFA in general and butyrate in particular enhance the growth of lactobacilli and bifidobacteria and play a crucial role in the colon physiology and metabolism (Roy et al, 2006). Total SCFA and regional differences in SCFA concentration are implicated in colon diseases, especially in cancer and gastrointestinal disorders, where disease often occurs distally. Therefore, an increased SCFA production and a higher delivery of SCFA distally, especially butyrate, may have a role in preventing these diseases.

Function and absorption of SCFAs

SCFAs are rapidly absorbed in the cecum and colon with only 5 % to 10 % being excreted in the feces. This process is associated with the enhanced sodium absorption and bicarbonate excretion. Two proposed mechanisms of absorption are: 1) diffusion of protonated SCFAs (at least 60 %) and 2) anion exchange (Cook and Sellin, 1998). SCFAs uptake is associated with the transport of water that seems to be higher in the distal than in proximal colon.

The major SCFAs: acetate, propionate, and butyrate are absorbed at comparable rates in different regions of the colon. Once absorbed, SCFAs are metabolized at 3 major sites in the body:

1) cells of the ceco-colonic epithelium that use butyrate as a major substrate for the maintenance of energy producing pathways;

2) liver cells that metabolize residual butyrate with propionate used for gluconeogenesis; 50 % to 70 % of acetate is also taken up by the liver;

3) muscle cells that generate energy from the oxidation of residual acetate.

The role of SCFAs has expanded to include their role as nutrients for the colonic epithelium, as modulators of colonic and intracellular pH, cell volume, and other functions associated with ion transport, and as regulators of proliferation, differentiation, and gene expression (Cook and Sellin, 1998). Increases in SCFAs result in the decreases of pH, which indirectly influences the composition of the colonic microflora, decreases solubility of bile acids, increases absorption of minerals (indirectly), and reduces the ammonia absorption by the protonic dissociation of ammonia and other amines (i.e., the formation of the less diffusible NH_4^+ compared with the diffusible NH3) (Vince et al, 1978; Jackson 1983; Jenkins et al, 1987).

Acetate, propionate, butyrate

Acetate, the principal SCFA in the colon, is readily absorbed and transported to the liver, and therefore less metabolized in the colon. The presence of acetyl-CoA synthetase in the cytosol of adipose and mammary glands allow the use of acetate for lipogenesis once it enters the systemic circulation. In human studies, acetate is often used to monitor colonic events because it is the main SCFA in the blood. Acetate is the primary substrate for cholesterol synthesis. In the host, it may be absorbed and utilized by peripheral tissues (Pomare et al, 1985), further, bacteria isolated from the human intestine are capable of utilizing acetate for the production of butyrate in the colon (Duncan et al, 2002). Lactate and acetoacetate may form substrate for other members of the flora and may be degraded into other SCFA.

Propionate is produced via 2 main pathways: 1) fixation of CO_2 to form succinate, which is subsequently decarboxylated (the "dicarboxylic acid pathway"); 2) from lactate and acrylate (the

"acrylate pathway"), (Cumming, 1981). Much of the knowledge about the nutritional fate of propionate comes from studies of ruminants. Intestinal glucose uptake is minimal in ruminants because of the presence of microbiota in their rumen for the digestion and fementation of carbohydrates. Production of SCFA constitutes the major source of ruminant energy (Hooper et al, 2002) where propionate is a primary precursor for gluconeogenesis. Propionate metabolism in humans is less understood. A number of mechanisms have been suggested to be responsible for the observed lipid lowering effect, with an increased propionate production being one of the possible mechanisms. Increased production of propionate, through fermentation, may inhibit hepatic cholesterol synthesis. It seems possible that one of the determinants of the actions of propionate on serum lipids is the ratio of propionate to acetate (Cheng and Lai, 2000; Wolever et al, 1996).

Butyrate is the preferred energy source of colonocytes and has been implicated in the control of the machinery regulating apoptosis and cellular proliferation and differentiation. 70 % to 90 % of butyrate is metabolized by the colonocyte (Zoran et al, 1997; Basson et al, 2000; Della Ragione et al, 2001). Sodium butyrate exerts an antiproliferative activity on many cells types, that have demonstrated preventive effects of butyrate on colon cancer and adenoma development (Bornet et al, 2002). At a molecular level, butyrate affects gene expression via the phosphorylation and acylation of histone proteins (Archer and Hodin, 1999). Butyrate is not produced by the lactic acid bacteria, however, certain probiotics may modify the ratio of SCFA in the colon. This remains one of their likely mechanisms of anti-carcinogenic action within the colon. Butyrate also stimulates immunogenicity of cancer cells.

There is a mounting evidence that SCFAs play a key role in colonic health and may play a key role in the prevention and management of certain diseases. Given the potential benefits of prebiotics and probiotics, this has added another dimension to the study of SCFAs. Now, there is a need for further studies examining the synergistic effects of the combination of functional foods from different carbohydrate surces and their effects on SCFA and health. The combination of in vitro, experimental and clinical trials will help to guide future dietary recommendations.

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