Beneficial health effects of low-digestible carbohydrate consumption

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Low-digestible carbohydrates represent a class of enzyme-resistant saccharides that have specific effects on the human gastrointestinal tract. In the small bowel, they affect nutrient digestion and absorption, glucose and lipid metabolism and protect against known risk factors of cardiovascular disease. In the colon they are mainly degraded by anaerobic bacteria in a process called fermentation. As a consequence, faecal nitrogen excretion is enhanced, which is used clinically to prevent or treat hepatic encephalopathy. Low-digestible carbohydrates are trophic to the epithelia of the ileum and colon, which helps to avoid bacterial translocation. Short-chain fatty acids are important fermentation products and are evaluated as new therapeutics in acute colitis. They are considered in the primary prevention of colorectal cancer. The bifidogenic effect of fructo-oligosaccharides merits further attention. Unfermented carbohydrates increase faecal bulk and play a role in the treatment of chronic functional constipation, symptomatic diverticulosis and, possibly, the irritable bowel syndrome. In conclusion, low-digestible carbohydrates may play a role in the maintenance of human digestive health. However, the strength of evidence differs between disease entities.

Low-digestible carbohydrates: Dietary fibre: Non-starch polysaccharides: Short-chain fatty acids: Total parenteral nutrition: Colorectal cancer

Introduction

Recently, Burkitt’s hypothesis (Burkitt, 1971) of primary prevention of colorectal cancer by dietary fibre has been challenged by data from the Nurses’ Health Study (Fuchs et al. 1999), which did not support the existence of an important protective effect of dietary fibre (DF) against colorectal cancer or adenoma. Consequently, the complex issue of potential health benefits provided by low-digestible carbohydrates (LDCs) has become more controversial. On the other hand, plausible mechanisms have been demonstrated by which LDCs interact with the gastrointestinal tract and which may explain their protective role in various Western diseases. In this concise review the evidence of possible links between LDC consumption and human health is presented.

LDCs in the gastrointestinal tract

Low-digestible carbohydrates represent a heterogeneous group of substances. They have in common a resistance against enzymatic degradation in the small intestine. In a complex fashion they interact with the digestion and absorption of nutrients in the small gut. Once LDCs reach the colon, their fate is determined by their bacterial fermentability. Short-chain fatty acids which are produced as endproducts of anaerobic carbohydrate breakdown affect the colonic epithelium in various ways. Other less-degradable fibre constituents act especially on the distal colon by their water-holding capacity, which is associated with a faecal bulking effect. Fig. 1 presents a summary of regional LDC effects and possibly related health benefits.

LDCs and vascular disease

The ‘metabolic syndrome’ comprises several risk factors that interact in a complicated and poorly understood fashion in the pathogenesis of cardiovascular disease: obesity, non-insulin dependent diabetes mellitus, combined hyperlipidaemia, and hypertension. There is evidence that LDCs may affect any of these risk factors.

The epidemiologic Health Professionals’ Study (Rimm et al. 1996) suggested an inverse association between fibre consumption and myocardial infarction. The relative risk of infarction was most effectively reduced by high cereal fibre intake. The protective effect of fibre persisted after correction for fat intake, i.e. fibre did not simply act by substituting fat in the diet. In other cohorts similar data were obtained (Khaw & Barret-Connor, 1987; Humble et al. 1993). Thus, fibre per se reduced the risk of coronary heart disease and was not simply an indicator of a healthy lifestyle.

The lack of fibre in the diet may be a contributing factor in obesity. In overweight subjects, the intake of fibre has been found significantly reduced, compared with lean control persons (Alfieri et al. 1995). Consequently, a fibre-rich diet has been advocated in the treatment of obesity.

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Fibre may facilitate compliance with low-energy diets by causing early satiety secondary to gastric distension. Jenkins et al. (1981) have introduced the glycaemic index to determine the effect of various food items on the postprandial blood glucose concentration. Although this approach simplifies the complex process of gastrointestinal digestion and absorption, the index has proved useful in the clinical setting. Fibre-rich foods are usually associated with a low postprandial blood glucose rise. Concerning fibre supplements, primarily gel-forming guar has been shown to delay small-intestinal glucose absorption, either by inhibiting the diffusion of glucose within the chyme (Blackburn et al. 1984) or by increasing the unstirred water layer (Blackburn & Johnson, 1983). The principle of slowing carbohydrate absorption (‘lente carbohydrate’) may have beneficial metabolic effects in diabetes and is considered in nutritional recommendations from diabetes societies (Töller et al. 1999).

Some soluble fibre constituents, e.g. oat bran, exhibit a modest cholesterol-lowering effect (reduction of total serum cholesterol by 5–15 % of the initial value). The mechanism of action is not entirely clear; fibre may act by interfering with cholesterol absorption or affecting bile acid metabolism. Another explanation could be the production of propionate during bacterial LDC fermentation in the colon which is absorbed into portal blood and reduces hepatic cholesterol production in experimental animals (Kasper, 1988). There is also evidence that some LDCs (e.g. fructo-oligosaccharides) lower plasma triglyceride concentrations (Agheli et al. 1998). For clinical purposes, it can be stated that soluble fibre makes a small but significant contribution to dietary therapy of hypercholesterolaemia (Brown et al. 1999).

In the Nurses’ Health Study (Ascherio et al. 1992) as well as in the Health Professionals’ Study (Ascherio et al. 1996) it has been found that an increased intake of fibre (and magnesium) was inversely associated with self-reported systolic and diastolic blood pressures. A high fibre consumption reduced the relative risk of stroke among hypertensive men significantly (Ascherio et al. 1998). In spontaneously hypertensive rats a high-fibre and low-fat diet reduced systolic and diastolic pressure values by 10–15 mmHg (Bagger et al. 1996). It is not known which fibre component is most effective in lowering elevated blood pressure.

In conclusion, a high-fibre diet can reduce several risk factors associated with cardiovascular disease although the underlying mechanisms of action are not well understood.

**LDCs and prebiotic effects**

Prebiotics are defined as ‘non-digestible food ingredients that beneficailly affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon’ (Gibson & Roberfroid, 1995) as opposed to probiotics that can be defined as viable cultures of micro-organisms that benefit the host by improving the qualities of the indigenous microflora (Havenaar et al. 1992). Among the LDCs, fructo-oligosaccharides occupy a key position by their ability to change significantly the composition of the colonic microflora. They stimulate selectively the growth of bifidobacteria (‘bifidogenesis’) in experimental animals and also in human volunteers making these bacteria the predominant genus in faeces (Gibson et al. 1995). A well-tolerated daily dose (10 g) of short-chain fructo-oligosaccharides is sufficient to increase significantly faecal bifidobacteria in healthy subjects (Bouhnik et al. 1999). Owing to this property fructo-oligosaccharides are classified as prebiotics.

A number of health benefits may be associated with bifidogenesis. Possibly detrimental bacteria, e.g. clostridia, may be displaced by bifidobacteria. The gut barrier function may be strengthened and the invasion of
pathogens prevented (Catala et al. 1999). The stimulation of the gut-associated immune system by prebiotics has been discussed. By releasing n-butyrate into the colonic lumen or alternative mechanisms bifidobacteria may affect the carcinogenic process (see below). Other health claims are related to carbohydrate and lipid metabolism of the macro-organism. Although interactions between fructo-oligosaccharides and functions of the large intestine are of scientific interest it has still to be proven that they contribute to human health (Roberfroid, 1997).

LDCs and hepatic encephalopathy (Fig. 1)

Lactulose, a synthetic disaccharide consisting of fructose and galactose subunits, has been widely used since 1966 in the treatment of hepatic encephalopathy (Bircher et al. 1966). This complication of advanced liver disease occurs as a consequence of reduced hepatic clearance of nitrogenous compounds (ammonia and others) which have entered the portal bloodstream mainly from the colon. When the colonic flora metabolizes lactulose, bacterial incorporation of nitrogen increases as does the bacterial mass. The administration of lactulose to humans causes an increase in faecal nitrogen and reduction of luminal ammonia concentrations (Fig. 2). The fermentation of carbohydrates results in the production of short-chain fatty acids (SCFAs) which reduce the diffusion of ionized ammonia into the portal blood in an acid environment (Weber et al. 1987).

Other LDCs, particular those contained in dietary fibre or resistant starch, seem to have similar effects to those of lactulose. In a faecal buffered homogenate in vitro, pectin, various starches and lactulose gave similar results in reducing ammonia concentrations (Aminosharie & Weber, 1993). In lactase-deficient subjects, especially in third world countries, the drinking of milk is another possible way to increase faecal nitrogen excretion (Uribe-Esquível et al. 1997). Likewise, the administration of a glucosidase inhibitor (e.g. acarbose) stimulates fermentation and contributes to faecal nitrogen excretion (Scheppach et al. 1988). These interventions are powerful tools to suppress hepatic encephalopathy in cirrhotic patients.

LDCs, colonic mucosal proliferation and the gut barrier

Dietary fibre components (especially those which are highly fermentable) are trophic to the colonic epithelium of rats, as shown by an increase in mucosal DNA, RNA, and protein content (Jacobs & Lupton, 1984). The same effect occurs when starch is malabsorbed and serves as a fermentable substrate to the microflora. Inert bulk (kaolin), however, does not affect the crypt cell production rate of mouse colonic mucosa (Goodlad & Wright, 1983). The proliferative effect of fibre on rat colonicocytes is seen in conventional but not in germ-free animals (Goodlad et al. 1989). It can be concluded from this finding that products of fibre breakdown and not fibre per se stimulate cell proliferation. Indeed, SCFAs enhance colonic mucosal proliferation in vivo (Kripke et al. 1989) and in vitro (Scheppach et al. 1992).

This trophic effect may be physiologically important if it improves large intestinal function under certain stress conditions. This issue was addressed in a series of rat studies. Colonic infusion of SCFA accelerated wound healing after colonic transection and re-anastomosis. Spontaneous anastomotic dehiscence was significantly less in the SCFA than in the control group; the anastomotic suture line burst in fewer colons from the SCFA group when tension was applied to the bowel wall (Rolandelli et al. 1986). After 80% small-bowel resection (i.e. in a model of the short-bowel syndrome) pectin (a highly fermentable dietary fibre) enhanced intestinal adaptation by increasing colonic mucosal DNA, RNA, and protein contents (Koruda et al. 1986); this resulted in a less pronounced postoperative weight loss than under control conditions. Summarizing these data from animal studies, there is evidence that the trophic effect of SCFA may enhance intestinal adaptation to surgical stress. To date, it is unclear if these effects obtained in animal experiments can be translated into improved postoperative performance of patients receiving enteral formula diets fortified with fibre.

A complex system with interrelated factors prevents the penetration of the small and, more importantly, the large intestinal wall by bacteria: the gut barrier. Little is known about the effect of fibre or its degradation products on the gut-associated immune system. There is a preliminary report showing stimulated DNA synthesis by lymphocytes in vitro in the presence of sodium butyrate (Carpaneto et al. 1991). Unspecific epithelial defences may also add to the gut barrier function. In the rat model, the effect of fibre on bacterial translocation from the gut to mesenteric lymph nodes, liver, and spleen has been tested. The addition of cellulose to an orally administered total parenteral nutrition (TPN) solution reduced the incidence of bacterial translocation (compared with TPN alone) (DaZhong & Deitch, 1998); supplementation with citrus pectin had no effect in this experimental setting (Spaeth et al. 1990). The addition of corn cobs, but not soy fibre, to a defined fibre-free formula diet reduced the translocation rate significantly (Alveryd et al. 1990). Both glutamine and fibre (psyllium), when added to a fibre-free formula diet, prevented loss of bowel mass, but neither substance protected effectively against spontaneous or endotoxin-induced bacterial translocation (Barber et al. 1990), a phenomenon primarily
noted in experimental animals. It seems that less fermentable fibre components are most effective concerning the prevention of translocation. No information is available concerning potentially protective effects from resistant starch or oligosaccharides. The applicability of these data to the clinical setting is uncertain, although translocation has been shown to occur in humans and to be associated with the likelihood of sepsis (Sedman et al. 1994).

**LDCs and colitis**

The idea that SCFAs may play a role in distinct forms of colonic inflammation was derived from Roediger’s fundamental experiments in isolated colonocytes. He showed that luminal n-butyrate produced during bacterial carbohydrate fermentation was the main luminal source of energy for these cells and was preferred over glutamine or glucose (Roediger, 1980a). He also demonstrated a limited ability of colonocytes in ulcerative colitis to oxidize SCFAs despite their abundance in the colonic lumen (Roediger, 1980b). From these and other observations Roediger set up the hypothesis of ‘nutritional colitis’: when luminal nutrition (by SCFAs) is inadequate during oral starvation colonic mucosal atrophy develops after a few days. Due to reduced absorptive capacity of the malnourished epithelium diarrhoea occurs which is even worsened by rapid refeeding. Prolonged mucosal starvation may not only lead to functional but also to structural changes such as ulceration. Inflammation of the mucosa may (at least partly) be due to a lack of luminal SCFAs (e.g. diversion colitis) or a diminished capacity of the mucosa to oxidize SCFAs (e.g. ulcerative colitis) (Roediger, 1990). Recently, anti-inflammatory effects of butyrate have been described; *in vitro*, butyrate inhibits the activation of nuclear factor kappa B which is a critical transcription factor of pro-inflammatory cytokines (Luehrs et al. 1999).

This intriguing hypothesis has prompted a number of empirical clinical trials testing SCFAs as a cure for distinct forms of colitis. SCFAs have been tested as a cure for diversion colitis, pouchitis and radiation proctitis; the majority of trials, however, have been performed in ulcerative colitis.

As no slow release formulation for oral use is available, trials using rectal enemas have been confined to proctitis, proctosigmoiditis or left-sided ulcerative colitis (Spechh et al. 1996; Breuer et al. 1997). Most of nine studies reported so far suggest a benefit from SCFAs, although lack of a control arm and small sample size has been criticized in some studies. Obviously, a large confirmatory trial is needed to finally assess this new mode of treatment which would be free of side-effects and cost saving. It has been learned from the pilot studies that patients with new onset of disease or after prolonged periods of remission may respond best. Trial periods should extend over six weeks and include enemas twice daily. The optimum composition of the enemas (mixture of SCFAs, butyrate monotherapy, combination with 5-aminosalicylic acid) has not yet been established (Cummings, 1997).

**LDCs and colorectal carcinogenesis**

The fibre hypothesis has originally been proposed by Denis Burkitt who found low incidence rates of colorectal cancer (CRC) in rural Africans consuming a high-fibre diet (Burkitt, 1969). Two meta-analyses of case-control studies reported a significant reduction of CRC risk with increasing consumption of dietary fibre (Trock et al. 1990; Howe et al. 1992). Prospective cohort studies, however, found no association between fibre consumption and cancer risk (Willett et al. 1990; Fuchs et al. 1999). The evidence of dietary fibre and CRC risk has recently been evaluated at a consensus conference sponsored by the World Health Organization (Scheppach et al. 1999).

Experimental studies have revealed that, together with non-starch polysaccharides (NSP), a major component of dietary fibre, resistant starch reaches the colon. On a high-starch diet, the amount of starch in the colon may even exceed the amount of NSP (Macfarlane & Cummings, 1991). Due to the lack of food-composition data the epidemiological evidence relating resistant starch with cancer risk is currently insufficient (Cassidy et al. 1994).

In animal experiments, fructo-oligosaccharides reduce the occurrence of aberrant crypt foci and colonic tumours (Pierre et al. 1997; Reddy et al. 1997). It is unknown whether this effect is due to increased numbers of bifidobacteria, enhanced butyrate production or other mechanisms.

Complex carbohydrates (NSP, resistant starch, oligosaccharides) are broken down by the microflora to SCFAs. There is growing experimental evidence that SCFAs, particularly n-butyrate, could have a protective role in the carcinogenic process by their effects on proliferation, apoptosis and gene expression (Fig. 3).

Normal proliferation of colonocytes occurs in the basal 60% of the crypts. In the upper 40% of the crypts, however, proliferation stops and colonocytes become fully differentiated, to be extruded after approximately 7 days of upward migration. The expansion of the proliferative compartment to the crypt surface (hyperproliferation, involving the upper 40% of the crypt length) is considered a neoplastic biomarker. Butyrate diminishes hyperproliferation in colonic mucosa obtained from patients with ulcerative colitis, a disease with well-known neoplastic potential (Scheppach et al. 1997). In uninflamed mucosa, butyrate antagonizes hyperproliferation that has been induced by incubation with cocarcinogenic deoxycholic acid (Bartram et al. 1993).

A disruption of the balance between cell gain through mitosis and cell loss through programmed cell death (apoptosis) is thought to be an important event in carcinogenesis. Hague et al. (1993) have found apoptosis to be increased when colonic adenoma and carcinoma cells were incubated with butyrate. The effect was less pronounced with decreasing chain length (n-butyrate>" propionate">acetate) (Hague et al. 1995). The action of SCFAs may be due to increased expression of genes that favour apoptosis (Bax, Bak) and, concomitantly, a reduced expression of counterplayers that prevent apoptosis (Bcl-2, Bcl-XL) (Hague et al. 1997; Schauber et al. 1999). Important links between butyrate, the inhibition of
Butyrate, Prop, and Ac compete for the binding sites on histone complexes in various cell lines. Early trials have focused on the effects of butyrate on proliferation and differentiation of neoplastic cells at the molecular level. Early trials have focused on the effects of butyrate on proliferation and differentiation of neoplastic cells at the molecular level. Early trials have focused on the effects of butyrate on proliferation and differentiation of neoplastic cells at the molecular level. Early trials have focused on the effects of butyrate on proliferation and differentiation of neoplastic cells at the molecular level. Early trials have focused on the effects of butyrate on proliferation and differentiation of neoplastic cells at the molecular level. Early trials have focused on the effects of butyrate on proliferation and differentiation of neoplastic cells at the molecular level. 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Western countries whereas it is rarely found in the Third World. It was suggested almost 30 years ago that this condition is a dietary deficiency disorder caused by an inadequate intake of dietary fibre. This view has recently been supported by investigators of the Health Professionals’ Study who found that a diet low in total dietary fibre increased the risk of symptomatic diverticular disease (Aldoori et al. 1994). Colonic diverticulosis is more prevalent in non-vegetarians than in vegetarians (Gear et al. 1979). Experimental animals on a low-fibre diet develop diverticula more frequently in their lifetime than those on a high-fibre diet (Fisher et al. 1985). Once established, diverticula do not disappear when a person receives a fibre supplement. However, symptoms associated with diverticulosis (abdominal pain, straining on defaecation) are improved after administration of bran fibre (Brodribb & Humphreys, 1976).

In Europe and the United States the irritable bowel syndrome (IBS) is a frequent condition affecting about 20 % of the adult population. Its diagnosis is based on identifying positive symptoms consistent with the condition (‘Rome criteria’) and excluding other conditions with similar clinical presentations. For a subgroup of patients with predominant constipation increased dietary fibre intake is recommended (Drossman et al. 1997). The scientific evidence for this recommendation, however, is weak. In two randomized crossover studies the control groups had symptomatic improvement similar to that of the treatment groups (bran, corn fibre) (Lucey et al. 1987; Cook et al. 1990).

Taking all this information together, low-digestible carbohydrates probably confer intestinal health benefits in various ways. However, the strength of evidence relating these saccharides with human pathology is different between diseases.

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