DIGESTIVE FATE OF SUGARS AND STARCHES - CONSEQUENCES FOR TISSUE METABOLISM AND HEALTH

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Summary

After languishing in the scientific wings for many years, starches and sugars are now centre stage in attempts to understand relationships between diet and health. In this paper I review the evidence that rate, extent and site of digestion (or fermentation) of these carbohydrates may be critically important in terms of tissue metabolism and human health. Reaven's hypothesis (Syndrome X) provides the context for investigations of the extent to which dietary carbohydrates can be used to increase insulin sensitivity and thus contribute to strategies for reducing the risk of non-insulin-dependent diabetes, hypertension and coronary artery disease. The suspicion that colonic fermentation plays a major role in the aetiology of large bowel disease has stimulated research on the normal physiology of this organ. Fermentation of starch resistant to pancreatic a-amylase and other carbohydrates may increase production of butyric acid, a molecule which regulates gene expression and colonocyte differentiation and which may protect against colorectal cancer.

I. INTRODUCTION

In most human diets, carbohydrates contribute 40-65% of the total energy. Starches provide at least 40% of the carbohydrate energy with the remainder largely from sugars. Non-starch polysaccharides (NSP) are quantitatively a much smaller fraction (10-20 times less) than either starches or sugars. In spite of this there has been an enormous research effort on the role of NSP in human diets and much speculation on their possible health benefits whilst starches and sugars were seen merely as sources of energy with little specific metabolic or pathophysiological interest beyond the role of sugars in dental caries. The last few years have seen a resurgence of interest in the chemistry and digestive fate of starches and sugars and of their effects on tissue metabolism, the results of which suggest that a review of the role of these carbohydrates is timely.

II. THE SMALL INTESTINE

In his challenging Banting Lecture, Reaven (1988) proposed that resistance to insulin-stimulated glucose uptake and hyperinsulinaemia are early events in the aetiology of three major diseases of Western society, viz.,non-insulin-dependent diabetes mellitus (NIDDM), hypertension and coronary artery disease (CAD). That these diseases are related and, indeed, may occur in the same individual is undoubted but Reaven's (1988) important contribution was to suggest that it is the hyperinsulinaemic response to reduced insulin sensitivity which provides the mechanistic link (Syndrome X). His conclusion was that 'The most desirable situation is to

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be an insulin sensitive individual, thereby not dependent on the ability of the ß-cell to secrete large amounts of insulin' (Reaven 1988). This hypothesis has been extended by others (Frayne and Coppack 1992) in an attempt to explain the connection between central adiposity, insulin resistance and CAD. Whilst acknowledging that a significant proportion of the inter-individual variation in insulin sensitivity is genetically determined, Reaven (1988) argued that avoiding obesity and maintaining physical activity were practical approaches to reducing the risk of insulin insensitivity and its sequelae. The pioneering work of Himsworth (1935-6) showed that consuming high carbohydrate diets for a few as seven days improved insulin sensitivity in healthy young men. More recently interest has focused on the differential responses in blood glucose and insulin concentrations which accompany changes in the type of carbohydrate eaten.

Crapo and her colleagues provided one of the earliest demonstrations that the plasma glucose and insulin responses to a fixed oral dose of carbohydrate depend on the nature of carbohydrate. In general, complex carbohydrates (a synonym for starches in this context) elicited lower responses than did sugars (glucose and sucrose) in healthy adults (Crapo et al. 1976) whilst these differences were accentuated in patients with reduced glucose tolerance (Crapo et al. 1977) or NIDDM (Crapo et al. 1981). On the assumption that very good blood glucose control is an appropriate strategy to reduce the incidence of long term complications in diabetes, Jenkins et al. (1981) developed the glycaemic index procedure for classifying foods according to their effects on blood glucose. Glycaemic index was defined as 'the area under the blood glucose response curve for each food expressed as a percentage of the area after taking the same amount of carbohydrate as glucose' (Jenkins et al. 1981). Later, white bread was chosen as the reference food (Wolever et al. 1985). This was a considerable departure from the long-held view that total available carbohydrate in all foods except those high in sucrose was biologically equivalent (Truswell 1992) and stimulated interest in the rate, site and extent of carbohydrate digestion in the small bowel.

(a) Sugars

Glucose, the major monosaccharide in Western diets, is absorbed rapidly and completely from the proximal small intestine by passive diffusion and by the Na^+-glucose co-transporter (Hirst 1993). In contrast large doses of fructose, which is normally absorbed by facilitated diffusion, may result in some of the monosaccharide escaping from small intestine and entering the caecum (Cummings and Englyst 1992). Of the two common disaccharides, sucrose hydrolysis in the small bowel is rapid and complete but some lactose may reach the caecum even in individuals who are not overtly lactose intolerant (Barr et al. 1981, 1984). The digestive fate of oligosaccharides has been less well studied. There are no mammalian enzymes known to hydrolyse sugars of the raffinose family which, therefore, are assumed to flow in their entirety to the large bowel where they are probably rapidly fermented since they are not detected in faeces (Goodlad and Mathers 1990). Oligofructoses probably have a similar fate (Cummings and Englyst 1992).

(b) Starches

Most in vivo studies have used post-prandial changes in blood glucose concentration to monitor the rate of starch digestion in human subjects. Hydrolysis of starch by pancreatic amylase is slowed, and may be incomplete, if access to the substrate is hindered by the physical structure of food fragments reaching the small intestine (Wursch et al. 1986; Heaton et al. 1988). Read et al. (1986) produced an effective demonstration of the profound effect of mastication on glycaemic response when they compared post-prandial blood glucose curves in volunteers who swallowed foods without chewing or after thorough chewing. The composition of the ingested starch also influences glycaemia. Meals rich in amylose produced a lower postprandial glucose peak than did a similar amylopectin-rich meal (Behall et al. 1988) and this difference persisted after five weeks of consumption of the test diets (Behall et al. 1989). Perhaps of more importance was the significantly reduced insulin response to the amylose-rich

diets. Other meal constituents may also delay starch digestion. For example, adding the viscous polysaccharide guar gum to starchy test meals reduces glycaemia in man (Jenkins et al. 1978) probably by reducing both the rate of starch hydrolysis (Tinker and Schneeman 1989) and the rate of glucose absorption (Rainbird et al. 1984).

There is now incontrovertible evidence from ileal intubation (Stephen et al. 1983; Fourie et al. 1988), breath hydrogen (Calloway and Murphy 1968; Strocchi and Levitt 1991) and ileostomist (Englyst and Cummings 1985, 1986, 1987) studies that not all dietary starch is digested in the small intestine. Determination of the physiologically important features of starch digestion, viz., site, rate and extent in man, poses considerable practical difficulties and current characterisation which provides information on rate and extent of small bowel digestion, is based on in vitro protocols validated against the available in vivo data on extent of digestion only (Englyst et al. 1992; Muir and O'Dea 1993). Whilst this approach is a considerable advance, it does not obviate the need for detailed in vivo studies in man. The challenge is to develop experimental methods which will provide not only a description of metabolic responses (eg as blood metabolite or hormone concentration) but also quantitative data on site, rate and extent of starch digestion and its metabolic consequences. The more widespread availability of suitable stable-isotope technology should allow the development of non-hazardous protocols for such investigations. The underlying hypothesis is that by slowing the rate of carbohydrate digestion and consequently increasing the proportion of glucose absorbed from more distal sites, the requirement for insulin secretion will be reduced and insulin sensitivity increased. This is ample justification for undertaking the work but the hypothesis remains unproven.

III. THE LARGE INTESTINE

Until recently, the normal physiology of the large bowel was of little interest and the organ's function was considered to be merely as a secondary site of water and electrolyte absorption. Its contents are unsavoury, its high density of bacteria seemed ominous and its relative inaccessibility did not encourage investigation. The current belief that large bowel disease may be influenced by metabolism within the colonic lumen has stimulated extensive study of the organ and in particular of the role of bacterial fermentation. As yet, relatively little detailed work in human subjects has been possible because of the unavailability of appropriate protocols and whilst there are many encouraging leads and some hypotheses, there are few established facts.

(a) Substrate supply

Collection of ileal effluent from healthy ileostomists, preferably where proctocolectomy was performed for ulcerative colitis and who show no evidence of small bowel disease (Andersson 1992), is probably the best approach to determining quantitatively the substrate supply to the large bowel bacteria. It neglects, of course, endogenous supply of mucin and desquamated cells from the colonic mucosa. Of at least 40g of potentially fermentable organic matter flowing daily from the terminal ileum, at least half is carbohydrate. The greatest uncertainty is over the inputs of starches and sugars. Detailed studies with single starch-rich meals in ileostomists have indicated that the proportion of dietary starch escaping small bowel digestion (resistant starch) varies widely from < 1 (rice, bread) to 75% (bananas; Cummings and Englyst 1991). Although it has been proposed that approximately 10% of all starch in Western diets is probably resistant starch (Cummings and Englyst 1991), direct support for this proposal remains elusive.

(b) Fermentation of starches and sugars

Flourie et al. (1986) intubated the caecum of five healthy volunteers and infused a

suspension of 50g raw wheat starch over a 4h period. Caecal pH fell rapidly and stayed 1-2 pH units below pre-infusion levels for up to 12 h probably because of the accumulation of short chain fatty acids (SCFA) and lactic acid. Faecal output of starch increased by only 1g over the 4d following starch infusion and Flourie et al. (1986) concluded that virtually all of the starch had been fermented. Most other studies of large bowel starch fermentation have relied upon in vitro anaerobic incubation of the test substance with colonic bacteria (Englyst et al. 1987; Goodlad and Mathers 1988), invasive studies in animal models (Mathers and Dawson 1991; Mathers and Smith 1993) or analysis of stool, blood and breath in man (Cummings and Englyst 1991). Starch fermentation is usually characterised by an increased proportion of butyrate (Englyst et al. 1987; Scheppach et al. 1988; Mallett et al. 1988; Goodlad and Mathers 1988) but the dose of starch can have a profound effect on the pattern of SCFA (Mathers and Smith 1993). Much less is known about the fermentation of the oligosaccharides likely to form the major sugars reaching the large bowel. Goodlad and Mathers (1988) give SCFA data from raffinose fermentation in vitro, Hoshi et al. (1994) report caecal organic acids in rats fed galactosylsucrose and xylosylfructoside whilst Roberfroid et al. (1993) suggest stoichiometric relationships for fermentation of oligofructose produced by partial enzymatic hydrolysis of inulin. Since some oligosaccharides are believed to stimulate the establishment of a health-promoting gut flora (Kelly et al. 1994), further investigation of their digestive fate is anticipated.

(c) Biological effects of SCFA

(i) Energy

In health, about 98% of SCFA produced in the colon are absorbed (Cummings et al. 1987) and can be used as metabolic fuels. Butyrate appears to be a preferred substrate for colonocytes (Roediger 1980) whilst little propionate or butyrate gets beyond the liver in rats (Goodlad and Mathers 1990) and man (Cummings et al. 1987); porcine hepatocytes may be less effective in this respect (Goodlad and Mathers 1991). Absorption of SCFA from starch fermentation provides approximately half the metabolisable energy compared with absorption of the precursor glucose (Mathers, 1992).

(ii) Propionate and blood cholesterol

Stephen (1994) gives an excellent review of the possible effects of propionate on lipid metabolism. Most interest has focused on the possibility that by stimulating colonic propionate production blood cholesterol concentrations could be lowered, perhaps by inhibition of HMG CoA reductase which catalyses the rate-limiting step in the pathway of cholesterol synthesis. The evidence for this hypothesis is equivocal and in our studies in rats we have been unable to demonstrate any effect of feeding sodium propionate (alone or in combination with acetate and butyrate) on either blood cholesterol concentration or hepatic cholesterol synthesis rate measured in vivo by the tritiated water incorporation method (M.M.A.K. Khattak and J.C. Mathers, unpublished).

(iii) Butyrate, gene expression and colonocyte differentiation

It has been known for 30 years that SCFA and especially butyrate are trophic for the rumen mucosa (Tamate et al. 1962; Sakata and Tamate 1978) an effect which also applies to the rat (Sakata 1987) and human (Scheppach 1994) intestinal epithelia. The mechanism for this stimulation of cell proliferation has not been elucidated but considerable progress is being made in establishing a role for butyrate in regulation of gene expression and colonocyte differentiation (Kim et al. 1994).

Butyrate induces many changes in a wide variety of cell types (Table 1) but one initially incongruous finding is that it usually causes inhibition of cell proliferation in vitro. This apparent inconsistency may be resolved when it is recalled that:

(a) the cell lines used for these studies are, in general, transformed and butyrate treatment induces terminal differentiation and

(b) many of the in vivo models begin from a state of hypoproliferation.

Table 1. Cellular effects of butyrate which may be related to altered gene expression

1. *Alteration of the amount of a limited number of proteins:* In general, proteins characteristic of cell differentiation are induced.

2. *Inhibition of cell proliferation:* Usually arrest occurs at early G_1 phase and DNA synthesis is strongly inhibited in vitro.

3. *Alteration of cell morphology and ultrastructure:* With transformed cells, cancer-specific properties are suppressed and normal cytoskeleton and external matrix reappear.

Adapted from Kruh et al. (1994)

An hypothesis for the molecular mechanism of action of butyrate has been proposed by Kruh et al. (1994) who suggest that butyrate acts at two levels: The initial effect is to inhibit histone deacetylase resulting in hyperacetylation of histones and increased accessibility of DNA to factors controlling gene expression. Secondly butyrate, directly or indirectly, alters the binding of regulatory transacting proteins to specific DNA sequences which control the expression of the gene.

(iv) Resistant starch and colorectal cancer

Epidemiological evidence suggests that populations consuming higher starch diets have lower rates of colorectal cancer (Cassidy et al. 1994). Among the many possible explanations for this association are the potential benefits of an increased supply of starch to the large bowel and its fermentation to produce extra butyrate. When healthy volunteers consumed 45g Hylon VII/d (a high amylose maize starch containing 62% resistant starch), cytotoxicity of the aqueous phase of faeces was decreased (probably because of reduced production of secondary bile acids in the more acidic colon) and there was a concomitant reduction in epithelial proliferation in rectal biopsies (van Munster et al. 1994). An early event in colorectal carcinogenesis is the upward expansion of the proliferative compartment of the crypt and, indeed, this may form a useful preneoplastic biomarker. In vitro, butyrate reduces upper crypt cell proliferation in normal cells when the latter is induced by the co-carcinogenic secondary bile acid deoxycholate (Scheppach 1994). Butyrate may also influence tumorigenesis at a much later stage by inhibiting colonocyte secretion of urokinase which appears to be involved in control of cell migration and invasiveness (Young and Gibson 1994). A double-blind placebo-controlled randomised trial (The CAPP Study) of the long-term efficacy of resistant starch in delaying polyp formation and associated changes in crypt cell proliferation in young subjects with familial adenomatous polyposis (FAP) has recently begun in Europe. Since the germ-line mutation in the *APC* gene which characterises FAP occurs in about 60% of sporadic colorectal carcinomas (Powell et al. 1992) and the collection of other mutations is similar in the two conditions (FAP gene carriers are essentially on a fast track to cancer for which the only effective treatment at present is surgical removal of the colon), it is believed that the results of this investigation may be of relevance to sporadic colorectal cancer.

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