Recent Dietary Carbohydrate Utilization Research Provides Insights into the Health Effects of Glyconutritional Supplements

Robert K. Murrary, MD, PhD;* Robert Sinnott, PhD, MPH;** Jane Ramberg, MS;** John Hall, DDS; Stephan Boyd, MD, PhD**

*Professor (Emeritus), Department of Biochemistry, University of Toronto, Toronto, Ontario, M5S 1A8, Canada;
**Mannatech,™ Inc., 600 S. Royal Lane, Suite 200, Coppell, Texas, U.S.A. 75019

Presented at: the Scripps Center for Integrative Medicine 3rd Annual Natural Supplements Conference, La Jolla, California

INTRODUCTION

Many health care practitioners are not familiar with glyconutritional supplements. These products contain mixtures of carbohydrates frequently deficient in the modern diet, including various monosaccharides and polysaccharides containing α- and ß-glycosidic linkages. The composition of a patented glyconutritional supplement marketed by Mannatech™ Inc., Ambrotose® complex, is provided in Table 1.

Human case reports, retrospective and prospective studies, and clinical trials confirm that glyconutrients exert wide-ranging health benefits.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23] The means by which they exert their effects, however, are only partly understood. Postulated mechanisms have included:

(1) they make up for dietary deficiencies in various sugars vital for synthesis of glycoconjugates (i.e., glycoproteins, glycolipids and proteoglycans);

(2) some glyconutrients (e.g., mannose and fucose) have been found useful in the treatment of certain congenital disorders of glycosylation;

(3) they may competitively inhibit the attachment of certain viruses and bacteria to cells.

Because scientific understanding of the complex functions of the GI tract is rapidly growing, we conducted an extensive literature search investigating the possibility that additional mechanisms involving the gut might explain the wide-ranging health benefits of glyconutritional supplements.

TABLE 1.

The composition of Ambrotose® complex

INGREDIENT	CONSTITUENT CARBOHYDRATES
Arabinogalactan (gum)	Arabinose, galactose
Rice starch	Glucose (as amylose or amylopectin)
Aloe vera gel extract	Acetylated polymannan
Gum ghatti	Arabinose, galactose, glucuronic acid, mannose, xylose
Glucosamine HCl	Glucosamine
Gum tragacanth	Arabinose, fucose, galactose, galacturonic acid, rhamnose, xylose

METHODS

We conducted an extensive literature search of human utilization of both simple (e.g., monosaccharides and small oligosaccharides) and complex (e.g., polysaccharide fibers and gums) carbohydrates, focusing on the role of the gut, its commensal bacteria and its immune system.

RESULTS

Many publications were identified that add significantly to current thinking about human utilization of dietary carbohydrates.[24] These publications primarily centered around three key concepts (Figure 1):

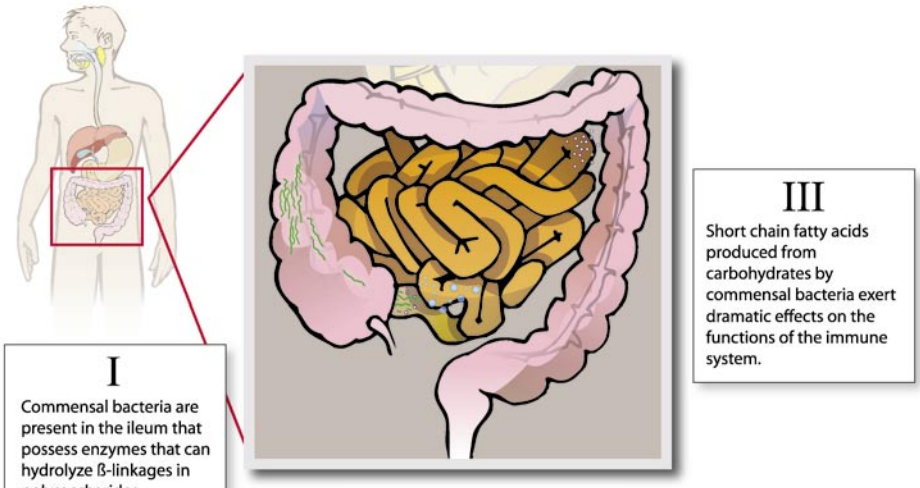
I. Commensal bacteria are present in the ileum that possess enzymes that can hydrolyze ß-linkages in polysaccharides.

Research in recent years has shown that the ileum contains a population of bacterial flora similar to that of the colon (Figure 2).[25] Only one enzyme derived from human gut cells is known to break ß-glycosidic linkages, thus limiting the liberation of a number of sugars from polysaccharides. Many bacteria contain a number of ß-glycosidases; one bacterium alone (Bacteroides thetaiotaomicron) possesses some eight enzymes that cleave these linkages.[26] Thus, polysaccharides can be broken down to oligosaccharides and monosaccharides in the ileum and further processed there.

II. Polysaccharides of commensal bacteria play an integral role in the proper development and function of the immune system.

It is estimated that approximately 70% of human immune cells reside in the gut wall.[27] The work of Mazmanian et al.[28] offers a dramatic example of the importance of one polysaccharide (polysaccharide A, PSac) present on the surface of Bacteroides fragilis in regulating the activity of the immune system. Using germ-free animals, these workers demonstrated that PSac directs the cellular and physical maturation of the developing immune system. It was able to correct systemic T cell deficiencies and T(H)1/T(H)2 imbalances and to direct lymphoid organogenesis. It also was able to elicit activation of CD4 cells and appropriate cytokine production. A summary of the mechanism of action of PSac is shown in Figure 3.[29]

Figure 1. Three key areas of involvement of commensal bacteria in the metabolism and function of carbohydrates in the human gut



I

Commensal bacteria are present in the ileum that possess enzymes that can hydrolyze ß-linkages in polysaccharides.

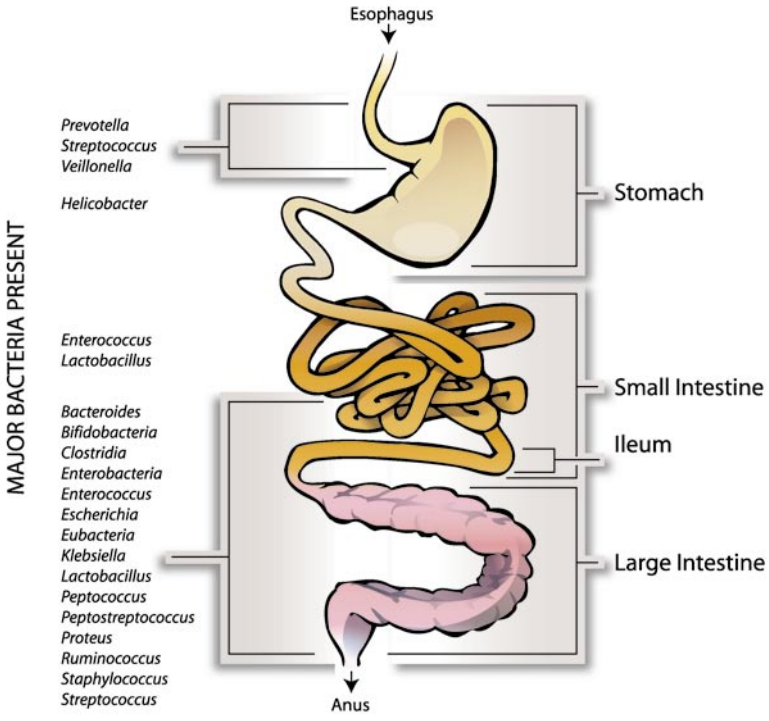
II

Polysaccharides of commensal bacteria play an integral role in the proper development and function of the immune system.

III

Short chain fatty acids produced from carbohydrates by commensal bacteria exert dramatic effects on the functions of the immune system.

Figure 2. Distribution of nonpathogenic microorganisms in healthy humans. Many of these bacteria possess enzymes that can cleave ß-glycosidic linkages



* Microbial Interactions with Humans. Chapter 21: 700-725. In: Madigan MT, Martinko JM. *Brock Biology of Microorganisms*. Pearson Prentice Hall, 2005.

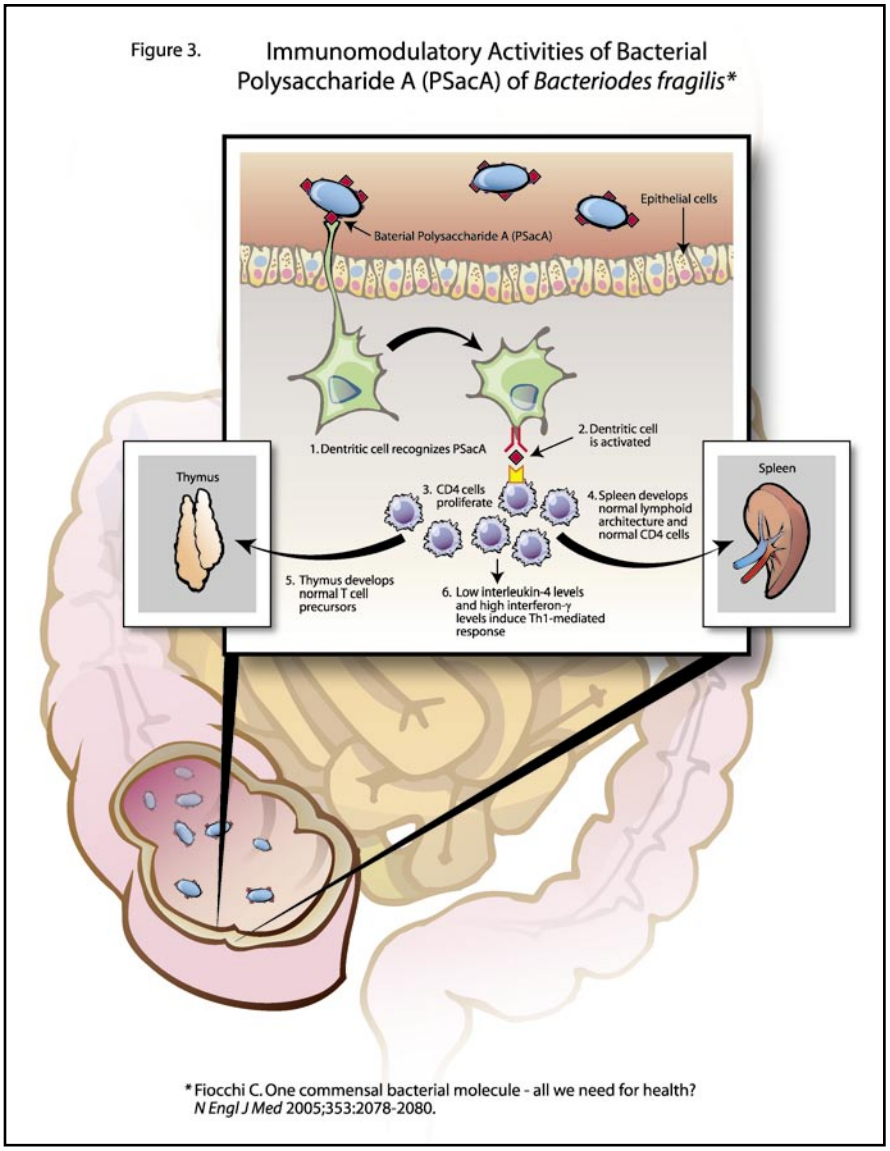


TABLE 2.

Some actions of butyrate, a short-chain fatty acid derived from the metabolism of carbohydrates by the actions of commensal bacteria.[12]

Diminishes production of mediators of inflammation by macrophages
Suppresses secretion of IL-8
Inhibits VCAM-1 mediated leukocyte adhesion to endothelial cells
Inhibits expression of ICAM-1 and VCAM-1 in endothelial cells
Enhances activation of peroxisomal proliferator activated receptor (PPAR)
Suppresses production of tumor necrosis factor-alpha

III. Short-chain fatty acids produced from carbohydrates by commensal bacteria exert dramatic effects on the functions of the immune system.

Commensal bacteria can degrade various carbohydrates to short-chain fatty acids (SCFAs).[30] The most important SCFA appears to be butyrate, a 3-carbon atom molecule, which has been found to exert a number of beneficial effects on the immune system (Table 2).

DISCUSSION

We have presented three examples of the complex relationships between carbohydrates, commensal bacteria and the gut:

(1) The presence of commensal bacteria in the ileum[25] has not previously been widely recognized. The ability of enzymes from these microorganisms to hydrolyze ß-glycosidic linkages in polysaccharides[26] greatly expands the spectrum of free monosaccharides to which the gut is exposed. Apart from providing substrates for synthesis of glycoconjugates, some of the released monosaccharides (e.g., mannose, rhamnose and galacturonic acid) may have novel biologic effects. Beneficial effects of commensal bacteria on many other processes (e.g., synthesis of certain B vitamins and vitamin K, etc.) are well known.[30]

(2) Polysaccharides present in commensal bacteria play important roles in modulating the immune system, as evidenced by the work on PSac, referred to above.[28] Indeed, it appears possible that exposure to polysaccharides in the gut after birth may be a major mechanism of initiating development of a normal immune system.

It is noteworthy that a polymannose (derived from Aloe vera), a major constituent of Ambrotose® complex (Table 1), has been shown to exert a variety of immunomodulatory effects.[24] Its actions may be similar to that of PSac.

(3) The production of the short-chain fatty acid butyrate from carbohydrates by commensal bacteria produces another type of molecule that also has important regulatory effects on the immune system.[24] The ability of butyrate to enhance the activation of peroxisomal proliferator activated receptor (PPAR) may help prevent ulcerative colitis and inhibit tumor progression.[31] By suppressing production of tumor necrosis factor-alpha, it may also benefit patients with rheumatoid arthritis.[32]

Two of the above examples directly involve the immune system. Further analysis of the interactions among carbohydrates, commensal bacteria, the gut and the immune system should be a fruitful area of research. This area also dovetails with the increasing interest in probiotics and prebiotics.

Our findings thus support the concept that the beneficial effects of glyconutrients are likely exerted by multiple mechanisms, many of which may involve the gut. Finally, we note that modern industrial societies have enjoyed a tremendous reduction in many infectious diseases of the gut. However, gastrointestinal and food allergies and inflammatory conditions of unexplained origin have increased dramatically.[33] We believe that significant changes from our pre-agricultural ancestors in hygiene and nutrient intake – particularly that of carbohydrates and bacteria – have played a significant role in the development of these conditions.[24]

REFERENCES

1. McKinley RN. The effect of dietary supplements on periodontal disease. J Am Nutraceutical Assoc. 1997;August (Suppl 1):21-24.
2. McKinley RN. Case report: effects of nutritional supplementation on benign mucous membrane pemphigus (cicatricial pemphigus). J Am Nutraceutical Assoc. 1997;August (Suppl 1):19-20.
3. McKinley RN. The effect of dietary supplements on herpes labialis. J Am Nutraceutical Assoc. 1997;August (Suppl 1):16-19.
4. Ganapini K. Dietary supplements improve many symptoms of asthma and decrease the need for other medications: a retrospective study. J Am Nutraceutical Assoc. 1997;August (Suppl 1):32-35.
5. Mondoa EI. Nutritional supplementation in recurrent otitis media: a case report. Proc Fisher Inst Med Res. 1999;1 (3):8-10.
6. Sweeney BF, McDaniel CF. Glyconutritional and phytochemicals in HCV-positive patients. Proc Fisher Inst Med Res. 1999;1 (3):6-7.
7. Nisinzweig S. Phytochemicals and glyconutrients in autistic children. Proc Fisher Inst Med Res. 1999;1 (3):12-14.
8. Kondraske G, Ward R. Case report: measurement of selected human athletic performance capacities before and after nutraceutical supplementation. Proc Fisher Inst Med Res. 2000;2 (1):9-12.
9. Gardiner T, McAnalley BH, Vennum EP. Glyconutritionals: consolidated review of potential benefits from the scientific literature. GlycoScience & Nutrition. 2001;2 (15):1-17.
10. DeJonge RA. Heart transplant patient's response to nutraceuticals. Proc Fisher Inst Med Res. 2001;2 (1):11-12.
11. Dykman KD, Gardiner T, and Ford CR. The effect of glyconutritional supplementation on toddlers with failure to thrive. Poster presentation at the Experimental Biology Annual Meeting, March 31-April 4, 2001.
12. Dykman KD, Gardiner T, Ford CR, et al. The effects of long-term supplementation on the functionality and use of non-drug therapies in patients diagnosed with fibromyalgia and chronic fatigue syndrome. Poster presentation at the Experimental Biology Annual Meeting, March 31-April 4, 2001.
13. Goux WJ, Boyd S, Tone CM, et al. Effect of glyconutritionals on oxidative stress in human subjects: a pilot study. GlycoScience & Nutrition. 2001;2 (12):1-10.
14. Schlachter M. Complex regional pain syndrome: a case presentation. Proc Fisher Inst Med Res. 2001;2 (2):10-10.
15. Schlachter M, Purcell B. Amyotrophic lateral sclerosis and nutritional supplementation: a case series. Proc Fisher Inst Med Res. 2001;2 (1):7-8.
16. Arcadi V. Case report: ataxic cerebral palsy multidisciplinary treatment effects including dietary supplementation. Proc Fisher Inst Med Res. 2002;2 (3):7-9.
17. Arcadi V. Case report: Prader-Willi: syndrome improvement with nutritional therapy and chiropractic care. Proc Fisher Inst Med Res. 2002;2 (3):11-13.
18. Hall J, Boyd S. Case report: improved tolerance of cancer therapy in a patient taking glyconutritional supplementation. GlycoScience & Nutrition. 2002;3 (2):1-4.
19. Pippenger CE, VanderWal M. Case study: free radical damage in marathon runners with and without glyconutritional supplementation. Proc Fisher Inst Med Res. 2003;3 (1):5-8.
20. Hipskind T. Effects of glyconutritionals on C-reactive protein ANA. Proc Fisher Inst Med Res. 2003;3 (1):11-13.
21. Boyd S, Gary K, Koepke CM, et al. An open-label pilot study of the antioxidant effect in healthy people of Ambrotose AO™. GlycoScience & Nutrition. 2003;4 (6):1-6.
22. Wang C, Szabo JS, Dykman RA. Effects of a carbohydrate supplement upon resting brain activity. Integr Physiol Behav Sci. 2004;39 (2):126-138.
23. Hipskind T. Effect of nutritional supplementation in peripheral neuropathy: a pilot study. Proc Fisher Inst Med Res. 2004;3 (2):13-15.
24. Ramberg J, Murray RK, Vennum E, et al. Dietary carbohydrates in the human GI tract: The established and emerging science. GlycoScience & Nutrition. 2005;6 (6):1-10.
25. Hao WL, Lee YK. Microflora of the gastrointestinal tract: a review. Methods Mol Biol. 2004;268:491-502.

26. Xu J, Gordon JI. Honor thy symbionts. Proc Nat Acad Sci USA. 2003;100 (18):10452-10459.
27. Bengmark S. Gut microbial ecology in critical illness: is there a role for prebiotics, probiotics, and synbiotics? Curr Opin Crit Care. 2002;8 (2):145-151.
28. Mazmanian SK, Liu CH, Tzianabos AO, et al. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell. 2005;122 (1):107-118.
29. Fiocchi C. One commensal bacterial molecule--all we need for health? N Engl J Med. 2005;353 (19):2078-2080.
30. Whitney E, Rolfes S. Understanding Nutrition. 9th Edition. Wadsworth/Thomson Learning: Belmont, Ca., 2002.
31. Kinoshita M, Suzuki Y, Saito Y. Butyrate reduces colonic paracellular permeability by enhancing PPARgamma activation. Biochem Biophys Res Commun. 2002;293 (2):827-831.
32. Fukae J, Amasaki Y, Yamashita Y, et al. Butyrate suppresses tumor necrosis factor alpha production by regulating specific messenger RNA degradation mediated through a cis-acting AU-rich element. Arthritis Rheum. 2005;52 (9):2697-2707.
33. Macdonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. Science. 2005;307 (5717):1920-1925.