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Prebiotics

DESCRIPTION

Prebiotics are defined as nondigestible food ingredients that may beneficially affect the host by selectively stimulating the growth and/or the activity of a limited number of bacteria in the colon. Thus, to be effective, prebiotics must escape digestion in the upper gastrointestinal tract and be used by a limited number of the microorganisms comprising the colonic microflora. Prebiotics are principally oligosaccharides. They mainly stimulate the growth of bifidobacteria, for which reason they are referred to as bifidogenic factors.

The following describes the various oligosaccharides which are classified as prebiotics.

FRUCTO-OLIGOSACCHARIDES

Fructo-oligosaccharides or FOS (see Fructo-Oligosaccharides) typically refer to short-chain oligosaccharides comprised of D-fructose and D-glucose, containing from three to five monosaccharide units. FOS, also called neosugar and short-chain FOS (sc FOS), are produced on a commercial scale from sucrose using a fungal fructosyltransferase enzyme. FOS are resistant to digestion in the upper gastrointestinal tract. They act to stimulate the growth of *Bifidobacterium* species in the large intestine. FOS are marketed in the United States in combination with probiotic bacteria and in some functional food products.

INULINS

Inulins (see Inulins) refer to a group of naturally-occurring fructose-containing oligosaccharides. Inulins belong to a class of carbohydrates known as fructans. They are derived from the roots of chicory *(Cichorium intybus)* and Jerusalem artichokes. Inulins are mainly comprised of fructose units and typically have a terminal glucose. The bond between fructose units in inulins is a beta-(2-1) glycosidic linkage. The average degreee of polymerization of inulins marketed as nutritional supplements is 10 to 12. Inulins stimulate the growth of *Bifidobacterium* species in the large intestine.

ISOMALTO-OLIGOSACCHARIDES

Isomalto-oligosaccharides comprise a mixture of alpha-D-(1→6)-linked glucose oligomers, including isomaltose, panose, isomaltotetraose, isomaltopentaose, nigerose, kojibiose, isopanose and higher branched oligo-saccharides. Isomalto-oligosaccharides are produced by various enzymatic processes. They act to stimulate the growth of *Bifidobacterium* species and *Lactobacillus* species in the large intestine. Isomalto-oligosaccharides are marketed in Japan as dietary supplements and in functional foods. They are being developed in the United States for similar uses.

LACTILOL

Lactilol is a disaccharide analogue of lactulose. Its pharmaceutical use is in the treatment of constipation and hepatic encephalopathy. Lactilol is also used in Japan as a prebiotic. It is resistant to digestion in the upper gastrointestinal tract and it is fermented by a limited number of colonic bacteria, resulting in an increase in the biomass of bifidobacteria and lactobacilli in the colon. Lactilol is known chemically as 4-0-(beta-D-galactopyranosyl)-D-glucitol. Lactilol is not approved for the treatment of hepatic encephalopathy or constipation in the U.S., and its use as a prebiotic is considered experimental. Lactilol is used in Europe as a food sweetener.

LACTOSUCROSE

Lactosucrose is a trisaccharide comprised of D-galactose, D-glucose and D-fructose. Lactosucrose is produced enzymatically by the enzymatic transfer of the galactosyl residue in lactose to sucrose. Lactosucrose is resistant to digestion in the stomach and small intestine. It is selectively utilized by intestinal *Bifidobacterium* species resulting in significant induction of growth of these bacteria in the colon. Therefore, under physiological conditions, lactosucrose acts on the intestinal microflora as a growth factor for *Bifidobacterium* species. Lactosucrose is also known as 4G-beta-D-galactosylsucrose. It is widely used in Japan as a dietary supplement and in functional foods, including yogurt. Lactosucrose is being developed in the United States for similar uses.

LACTULOSE

Lactulose (see Lactulose) is a semisynthetic disaccharide comprised of the sugars D-galactose and D-fructose. The sugars are joined by a beta-glycosidic linkage, making it resistant to hydrolysis by human digestive enzymes. Lactulose is, however, fermented by a limited number of colonic bacteria. This can lead to changes in the colonic ecosystem in favor of bacteria, such as lactobacilli and bifidobacteria, which may confer some health benefits. Lactulose is a prescription drug in the United States for the treatment of constipation and hepatic encephalopathy. It is marketed in Japan for use as a dietary supplement and in functional foods. Its use in the United States as a prebiotic substance is still experimental.

PYRODEXTRINS

Pyrodextrins comprise a mixture of glucose-containing oligosaccharides that is derived from the hydrolysis of starch. Pyrodextrins have been found to promote the proliferation of *Bifidobacterium* species in the large intestine. They are resistant to digestion in the upper gastrointestinal tract. Pyrodextrins are being developed for the nutritional supplement market place.

SOY OLIGOSACCHARIDES

Soy oligosaccharides refer to oligosaccharides found in soybeans and also in other beans and peas. The two principal soy oligosaccharides are the trisaccharide raffinose and the tetrasaccharide stachyose. Raffinose is comprised of one molecule each of D-galactose, D-glucose and D-fructose. Stachyose is comprised of two molecules of D-galactose, one molecule of D-glucose and one molecule of D-fructose. Soy oligosaccharides act to stimulate the growth of *Bifidobacterium* species in the large intestine. They are marketed in Japan as dietary supplements and in functional foods. They are being developed in the United States for similar uses.

TRANSGALACTO-OLIGOSACCHARIDES

Transgalacto-oligosaccharides (TOS) are a mixture of oligosaccharides consisting of D-glucose and D-galactose. TOS are produced from D-lactose via the action of the enzyme beta-galactosidase obtained from *Aspergillus oryzae*. TOS are resistant to digestion in the upper gastrointestinal tract and stimulate the growth of bifidobacteria in the large intestine. TOS are marketed in Japan and Europe as dietary supplements and are used in functional foods. They are being developed for similar use in the United States. (See Transgalacto-Oligosaccharides).

XYLO-OLIGOSACCHARIDES

Xylo-oligosaccharides are comprised of oligosaccharides containing beta (1→4) linked xylose residues. The degree of polymerization of xylo-oligosaccharides is from two to four. Xylo-oligosaccharides are obtained by enzymatic hydrolysis of the polysaccharide xylan. They are marketed in Japan as prebiotics and are being developed for similar use in the United States.

ACTIONS AND PHARMACOLOGY

ACTIONS

Prebiotics may have anticarcinogenic, antimicrobial, hypolipidemic and glucose-modulatory activities. They may also have activity in improving mineral absorption and balance and may have anti-osteoporotic activity.

MECHANISM OF ACTION

The possible anticarcinogenic activity of prebiotics is not well understood. It may be accounted for, in part, by the possible anticarcinogenic activity of butyrate. Butyrate, along with other short-chain fatty acids, is produced by bacterial fermentation of the various prebiotic oligosaccharides in the colon. Some studies suggest that butyrate may induce growth arrest and cell differentiation and may also upregulate apoptosis, three activities which could be significant for its possible anticarcinogenic activity. The prebiotic oligosaccharides may also aid in increasing the concentrations of calcium and magnesium in the colon. Elevated concentrations of these cations in the colon may help to control the rate of cell turnover. Elevated concentrations of calcium in the colon may help to control the formation of insoluble bile or salts of fatty acids. This might reduce the potential damaging effects of bile or fatty acids on colonocytes. The prebiotics may stimulate the growth of bifidobacteria and lactobacilli in the large intestine. There are *in vitro* and animal data suggesting that these bacteria can bind to and inactivate some carcinogens, can directly inhibit the growth of some tumors and can inhibit bacteria that may convert precarcinogens into carcinogens.

The possible antimicrobial activity of the prebiotics may be accounted for by their growth-promoting effects on bifidobacteria and lactobacilli. These bacteria can reinforce the barrier function of the intestinal mucosa, helping in the prevention of the attachment of pathogenic bacteria, essentially by crowding them out. These bacteria may also produce antimicrobial substances and stimulate antigen specific and nonspecific immune responses.

The prebiotics may lower triglyceride levels in some. The mechanism of this possible effect is unclear. Decreased hepatocyte *de novo* synthesis of triglycerides is one hypothetical possibility. The prebiotics may also lower total cholesterol and LDL-cholesterol levels in some. Again, the mechanism of this possible effect is unclear. Propionate, a product of oligosaccharide fermentation in the colon, may inhibit HMG-CoA reductase, the rate limiting step in cholesterol synthesis.

The possible effects of the prebiotics on blood glucose may be accounted for in a few ways. The oligosaccharides may delay gastric emptying and/or shorten small intestinal tract transit time. This may be via the short-chain fatty acids produced from the oligosaccharides in the colon. Short-chain fatty acids may be involved in the so-called "ileocolonic brake," which refers to the inhibition of gastric emptying by nutrients reaching the ileo-colonic junction. Short-chain fatty acids may also stimulate contractions of the ileum and shorten ileal emptying. In addition, propionate may inhibit gluconeogenesis by its metabolic conversion to methylmalonyl-CoA and succinyl-CoA. These metabolites could inhibit pyruvate carboxylase. Propionate may also reduce plasma levels of free fatty acids. High levels of free fatty acids lower glucose utilization and induce insulin resistance. Finally, propionate may enhance glycolysis via depletion of

citrate in hepatocytes. Citrate is an allosteric inhibitor of phosphofructokinase. In short, the mechanism of the possible effects of prebiotics on glucose tolerance are not well understood.

The oligosaccharides may bind/sequester such minerals as calcium and magnesium in the small intestine. The short-chain fatty acids formed from the bacterial fermentation of the oligosaccharides may facilitate the colonic absorption of calcium and, possibly, also magnesium ions. This could be beneficial in the prevention of osteoporosis and osteopenia.

PHARMACOKINETICS

Following ingestion, the prebiotic oligosaccharides reach the colon with very little of them being digested in the upper gastrointestinal tract. The oligosaccharides are fermented by bifidobacteria, lactobacilli and some other bacteria in the colon to produce the short-chain fatty acids acetate, propionate and butyrate; the gases hydrogen, hydrogen sulfide, carbon dioxide and methane; and lactate, pyruvate, succinate and formate. Acetate, propionate and butyrate that are not metabolized in colonocytes are absorbed from the colon and transported via the portal circulation to the liver. These short-chain fatty acids are extensively metabolized in hepatocytes. Acetate, propionate and butyrate that are not metabolized in hepatocytes are transported by the circulation to various tissues where they undergo further metabolism. Butyrate is an important respiratory fuel for colonocytes.

INDICATIONS AND USAGE

Some prebiotics are used, pharmaceutically, for the treatment of constipation and hepatic encephalopathy. Prebiotics may protect against some intestinal pathogens and may be helpful in some inflammatory bowel disease. They may have some anticarcinogenic effects and may exert favorable lipid effects in some. They may, in some instances, enhance mineral absorption and might help protect against osteoporosis. There is some preliminary research that certain prebiotics might be of some benefit in diabetes mellitus.

RESEARCH SUMMARY

Lactulose is a prescription drug in the United States. It is used to treat constipation and hepatic encephalopathy. Lactilol, similarly, is used pharmaceutically in Europe and elsewhere to treat the same conditions. These prebiotics, as well as several others, including transgalacto-oligosaccharides (TOS), fructo-oligosaccharides (FOS) and various of the experimental prebiotics, have shown benefits in favorably modulating the microbial ecology of the gut, protecting against various intestinal pathogens and, in some instances, boosting gastrointestinal immunity. Lactulose has exhibited some ability to ameliorate symptoms of idiopathic, as well as infectious, inflammatory bowel disease.

Both lactulose and inulins have suppressed experimentally induced colonic aberrant crypt foci in rats, and lactulose helped protect colonic mucosa against a known colon carcinogen in another study. FOS has also shown experimental anticarcinogenic effects, significantly reducing incidence of colon tumors, for example, in one animal study.

In one clinical study, patients who had undergone endoscopic removal of colorectal polyps were administered antioxidant vitamins or lactulose to see if these substances could reduce the recurrence rate of adenomatous polyps. The study continued for five years. During this period polyps recurred in 5.7% of those taking the vitamins (A, C and E) and in 14.7% of those taking lactulose. The recurrence rate in untreated controls was 35.9%.

TOS have exerted hypocholesterolemic effects in animals. They have also shown some preliminary, experimental ability to lower triglycerides. A fermented milk product containing FOS lowered LDL-cholesterol levels in male subjects with borderline elevated serum cholesterol levels in a double-blind, placebo-controlled study. There is a small study in which inulins reportedly lowered plasma total cholesterol and triglyceride levels significantly in healthy male volunteers. Results have been mixed, however, with respect to prebiotic effects on lipids, and more research is needed.

TOS have demonstrated positive effects on calcium absorption and have prevented bone loss in some animal research. Lactulose has significantly stimulated calcium absorption in postmenopausal women in preliminary clinical work.

Lactulose and some of the other prebiotics have also shown some ability to improve glucose tolerance and have other effects on carbohydrate metabolism that could prove helpful in some with diabetes mellitus. This research, too, is very preliminary and ongoing.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Prebiotics are contraindicated in those who are hypersensitive to any component of a prebiotic-containing supplement.

Some lactulose preparations contain galactose. Therefore, lactulose is contraindicated in those who require a low galactose diet.

PRECAUTIONS

In the United States, lactulose is a prescription drug. Its use requires medical supervision. Its use as a dietary supplement is considered experimental.

Those with lactose intolerance should exercise caution in the use of lactulose, lactilol and transgalacto-oligosaccharides.

Those who develop gastrointestinal symptoms (flatus, bloating, diarrhea) with the use of dietary fiber should exercise some degree of caution in the use of prebiotics. Those receiving whole body radiation or radiation to the gastrointestinal tract should avoid prebiotic supplements.

Pregnant women and nursing mothers should only use prebiotic supplements if prescribed by their physicians.

ADVERSE REACTIONS

Doses of prebiotic oligosaccharides up to 10 grams daily are well tolerated. Higher doses may cause gastrointestinal symptoms, such as flatulence, bloating and diarrhea.

INTERACTIONS

NUTRITIONAL SUPPLEMENTS

Alpha-galactosidase: Concomitant use of alpha-galactosidase (see Supplemental Enzymes) and soy oligosaccharides may decrease the effectiveness of the soy oligosaccharides.

Minerals (calcium, magnesium): Concomitant intake of calcium or magnesium and prebiotics may enhance the colonic absorption of these minerals.

Probiotics: Concomitant intake of probiotics and prebiotics may enhance the possible effectiveness of both the probiotics and the prebiotics.

FOODS

Prebiotic oligosaccharides may enhance the colonic absorption of calcium and magnesium in foods.

DOSAGE AND ADMINISTRATION

Fructo-oligosaccharides, (FOS) and inulins are available in nutritional supplements and in functional foods. Dosage is variable for both FOS and inulins and ranges from 4 to 10 grams. Those who use more than 10 grams daily of FOS or inulins should split the dosage throughout the day. Doses higher than 30 grams daily of FOS or inulins may cause significant gastrointestinal discomfort (flatulence, bloating, cramping, diarrhea).

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For additional Literature, see Fructo-Oligosaccharides, Inulins, Lactulose, Transgalacto-Oligosaccharides.

Pregnenolone

DESCRIPTION

Pregnenolone is a steroid naturally found in animal tissues, especially in the gonads, adrenal gland and brain. Pregnenolone is synthesized from cholesterol and is a precursor for the biosynthesis of steroid hormones. In the adrenal gland, pregnenolone is a precursor to the mineralocorticoid aldosterone, the glucocorticoid cortisol, as well as dehydroepiandrosterone (DHEA) and progesterone. In the ovary, pregnenolone is a precursor to estrogens and progesterone, and, in the testis, pregnenolone is a precursor to testosterone.

Pregnenolone and its metabolite pregnenolone sulfate are now known to be synthesized in the brain either *de novo* from cholesterol or from other metabolites. Pregnenolone and pregnenolone sulfate found in the brain and central nervous system are referred to as neurosteroids.

Pregnenolone is known chemically as 3-Hydroxypregn-5-en-20-one; delta 5-pregnen-3 beta-ol-20-one, and 17 beta-(1-