U.S. Dairy Export Council®

GUT HEALTH AND WHEY PRODUCTS

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This monograph reviews the scientific evidence and mechanisms which explain how whey products can support optimal gut health. The gut is critical to host nutrition through its role in the digestion and absorption of food. It also provides an essential barrier to the external environment, protecting against infection and disease. This barrier is not simply physical, but involves a complex mucosal immune system focused on maintaining a healthy gut.

Shortly after birth, the gut has not yet developed completely to fulfill its two main functions. The ingestion of milk, particularly specific components of the whey fraction, supports further development of the gut and enhances the barrier function. Immunoglobulins, lactoferrin, and other antibacterial components help to prevent intestinal infections, whereas oligosaccharides together with lactose favor the development of a healthy gut flora. A healthy gut flora enhances the colonization resistance against pathogens and produces useful components for the body.

This monograph deals with the ingestion of whey and whey components to promote gut health. It addresses this benefit particularly in view of the main functions of the intestine.

The intestinal tract is a complex organ system in the human body. It has two main functions: digestion of food and absorption of nutrients (1); a barrier against colonization and/or translocation of pathogens and against penetration into the body of toxic components. It is evident that these two functions, unified in one organ system, often conflict with each other and therefore require a highly specialized tissue organization. It should be stressed that since the inside of the gut is still the outside of the body, at the level of the intestine, the body is sensing the outside world and making decisions about absorption and rejection. The highly specialized structure of the gut for absorption is reflected by the enormous inner surface area of the small intestine, which is as large as a soccer field. This extension of the inner surface of the gut cylinder is brought about by special folds of the inner surface (folds of Kerckring) and the structure of villi and microvilli of the mucosa. The barrier function of the intestine includes the layer of epithelial cells, an extensive immune system called the gut associate lymphoid tissue (GALT), the intestinal flora, secretion of acid, bile, mucous and immunoglobulins, peristaltic movements and rapid turnover of epithelial cells.

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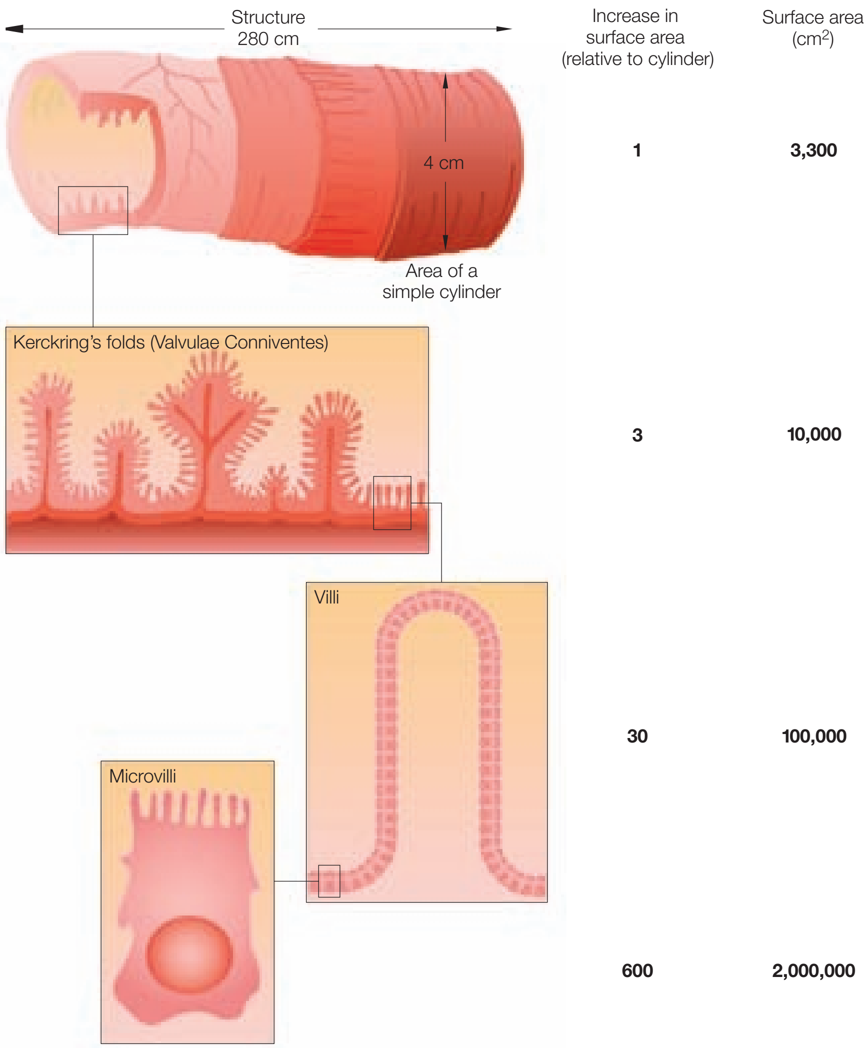
WHY IS WHEY A CANDIDATE TO SUPPORT GUT HEALTH?

Whey products are an excellent source of nutrients, providing high quality protein, lactose and minerals, as well as a wide range of bioactive components. Many of these bioactives are naturally occurring, and others can be obtained or enhanced through processing of whey by suppliers. Unique peptides and other components, with antimicrobial, anticancer and immunomodulatory properties can support or improve gastrointestinal health. Lactoperoxidase, immunoglobulins, peptide hydrolysates and growth factors are few of the trophic, health promoting factors found in, or obtained from whey (3).

Currently, the whey fraction is processed for different product specifications. These whey fractions can be characterized based on their protein content. A fundamental health benefit of whey proteins is that they are a valuable source of essential amino acids needed for growth and repair of tissues. The protein content of whey products range from 90%+ in whey protein isolate, 35-85% in whey protein concentrate or 11-14% in sweet whey powder. Additional product specifications include modified whey products or whey derivatives (at times called fractions), such as lactose-hydrolyzed or demineralized whey, α-lactalbumin, and lactoferrin (4). These ingredients are used in many food and nutritional products. The ability to further customize the components in whey products and to target specific populations to improve gut health is an exciting and emerging opportunity.

Some of the proposed roles for specific whey components that contribute to gut health include enhancing gut enzyme and microbial activity, physico-chemical conditions of the intestinal lumen, nutrient uptake and intestinal integrity.

Figure 1. Morphological Structure of the Intestine



Credit: Caspary W.S. 1992. Physiological and pathophysiology of intestinal absorption. *Am J Clin Nutr* 55:299S-308S. (For this figure Caspary refers to Wilson T.H. Intestinal absorption. Philadelphia: WB Saunders, 1962.)

HOW DOES THE INTESTINE FUNCTION?

It is important to realize the complexity and challenges that the intestine is faced with on a daily basis to fully appreciate its relationship to health. Optimal gut functioning requires that nutrient load is matched to the absorptive capacity to avoid the side effects of an improperly functioning gut such as bloating, gas, heartburn, diarrhea and/or constipation.

Structurally, the gastrointestinal tract is a tube that starts in the mouth and continues through to the anus. The inside of the tube is referred to as the intestinal lumen where ingested food mixes with bodily secretions and digestive enzymes; and interact with the intestinal wall to process and absorb the intestinal contents. Each segment of the gut has specific functions and structures to ensure efficient digestion and absorption; the gastrointestinal system is a highly coordinated one. As macronutrients are emptied from the stomach, they elicit specific reflexes to control motility and secretion. As contents hit the first part of the intestine, bicarbonate is secreted to neutralize stomach acid, the pancreas secrete digestive enzymes, bile is secreted into the small intestine, absorption of monosaccharides, amino acids, minerals and other nutrients begin and all these factors need to come together to maximize nutrient absorption.

The cells lining the intestinal lumen are the first point of contact between intestinal contents and the rest of the body. It is at this interface that nutrition, environment and genetics come together to determine gut health. Diet is a factor that can be extremely varied in terms of quantity, quality, frequency and duration of meals in individuals, but that can also be modified with targeted dietary interventions to produce the best results for any individual. A well functioning gut is necessary for good health, and a healthy diet is necessary to counteract genetic and environmental factors that may impact our general health (5).

One of the fundamental principles of gut physiology is that the epithelium is a selective barrier; the gut digests and absorbs dietary nutrients while preventing the passage of unwanted substances to the circulatory system. The intestinal wall consists of a single layer of epithelial cells and the continuity of this layer is critical to the proper functioning of the intestinal barrier. The epithelial layer is resting on a basement membrane, and the space between the epithelial cells and the muscle layers is called the lamina propria. It has neurons, blood vessels, lymphatic vessels and an extensive immune system that support gut function. The intestine has a critical role in immunity: about 70% of immune competent cells are found at the level of the intestine.

Within this layer of closely packed cells are the mechanisms that coordinate the absorption of dietary nutrients including protein, lipids, carbohydrates, water, vitamins and minerals. Food has to be broken down into absorbable components. Sugars are absorbed as monosaccharides; proteins as amino acids or di and tripeptides; and fat micelles as fatty acids and monoglycerides. There are specialized cells called goblet cells for secretion of mucus; paneth cells at the base of the crypt that secrete antimicrobial substances; and endocrine cells that secrete hormones and neurotransmitters for reflex control of food intake.

Each nutrient is absorbed through the intestinal wall by specific channels or transporters in the brush border membrane, which is the transcellular pathway or through the intercellular tight junctions that adjoin cells, the paracellular pathway. There are gradients of transporters along the gut; the highest concentration of the sodium glucose linked cotransporter is found in the duodenum and decreases down the length of the gut to the ileum (6). This transporter is not found in the colon as any free glucose will be absorbed prior to that in a healthy individual. Table 1 summarizes the literature on the amount each nutrient is absorbed; the range is from near complete absorption of lipid and simple carbohydrate sources, down to 2% of non-heme iron.

The apical surface of the intestine is lined with a brush border membrane (7). The brush border is composed of microvilli, finger-like projections that significantly increase the surface area of the cells that are in contact with the nutrients in the lumen. The brush border is rich in transporters, channels and some hydrolytic enzymes that are important in the ultimate absorption of dietary nutrients.

Polarization of the cell into an apical and basolateral side is critical for the transport of nutrients; polarization is accomplished by having the tight junctions that can be described as a ring around the cell that makes connections to the adjacent cells (8). In practical terms, this allows the cells to have a different complement of enzymes, channels and transporters on the apical and basolateral sides. The apical side is focused on getting nutrients into the cell and the basolateral side is focused on getting nutrients out of the cell into the lamina propria and the blood stream. Tight junctions operate to regulate the flow of elemental nutrients. Very few nutrients are small enough to fit through healthy tight junctions (Table 1).

Table 1. Bioavailability and Uptake of Selected Dietary Nutrients

Nutrient	Range of Bioavailability	Main Location of Uptake	Transcellular	Paracellular
Water	NA	Large Intestine	–	Yes
Protein	30-92% (derived from 9)	Small Intestine	Yes	–
Lipid (10)	95%	Small Intestine	Yes	–
Sucrose (11, 12)	100%	Small Intestine	100%	Negligible
Lactose	~5-95% (11)	Small Intestine	Yes	–
Calcium	5-35% (13)	Jejunum>Ileum	15%	85%
Magnesium (14)	~30% (15)	Ileum, Large Intestine	Yes	–
Iron (heme)	5-40% (16)	Small Intestine	Yes	–
Iron (non-heme)	2-45% (17)	Small Intestine	Yes	–
Phosphorus (18)	65-75% (19)	Intestine	Yes	Yes
Vitamin C (20)	70-90% to 50% or less with doses >1000 mg/d	Small Intestine	Yes	–
Folic Acid (21)	70%~	Small Intestine	Yes	–
Carotenoids (22)	<30%	With Lipids	Yes	–

HOW IS INTESTINAL FUNCTION MAINTAINED?

The intestine is constantly exposed to a harsh environment and one of the ways it is protected from damage and malignancy is that cells are constantly renewed. Cells are replaced approximately every 5 days, in which time they complete all stages of proliferation and differentiation and are finally shed into the lumen (23, 24). Development is regulated by crypt progenitors, the immortal stem cells located at the base of the intestine. Each crypt generates approximately 200 daughter cells per day providing a major driver for epithelial renewal, dividing every 12-16 hours resulting in the continuous upward movement of daughter cells (24). Cells from the crypt move up the crypt-villus axis along the basement membrane until they reach the villus tip where they are shed into the lumen. This process ensures that transport area and barrier resistance are maintained.

The brush border membrane of the small intestinal epithelial cells contains various hydrolytic enzymes to assist in the digestion of food. Most nutrients require specific enzymatic hydrolysis preceding intestinal absorption. Amylase is needed to hydrolyze starch to single sugar units, while trypsin and other proteases are needed for protein. Lipase, bile, cholesterol and other cofactors are needed for processing different triglycerides, free fatty acids, and long chain fatty acids in the intestinal lumen (Table 2). The process of digesting starch and fat is highly efficient in normal subjects and bioavailability is very high (Table 1). In the case of protein, accessibility to cleavage sites and size of the protein require more time to get to the absorbable unit; single amino acids and di and tripeptides are the only protein components to be actively transported across the gut wall. Lactose is a disaccharide whose enzyme activity decreases or is non-persistent in adults and may be instead used by resident bacterial flora to generate other nutrients for gut use. When lactose reaches the colon, it is fermented by the microflora there.

Table 2. Anatomical, Physical and Physiological Variables in the Human Gastrointestinal Tract (permission requested by author) (11)

Small Intestine Variables	Data
Transport area (without microvilli) in cm^2	~100,000
Luminal fluid volume (ml)	~9,000 entering duodenum per 24hr, mean 5250
Fluid load (uL(cm^2*h))	~2.2
Transepithelial resistance (R_t) ohms/cm^2	~25-50 in jejunum
Effective pore radius of tight junctions (Angstroms)	~6.7-8.8 in jejunum
Transepithelial potential difference ψ^{ms} (mV)	~0-3 in jejunum, 4-6 in ileum
Peak amylase output	~39kU/h
Peak trypsin output	~5-10kU/30min
Food stimulated lipase output	~4kU/min
Food stimulated bile salt output	~20uM/min
pH	~5.7-6.4 in the duodenum, up to ~7.4 in the jejunum, up to ~7.7 in the ileum
Peristaltic frequency	~11.7/min in the duodenum, 8.9-9.8/min in the jejunum and ileum
Luminal osmolality (mosmol/kg H_2O)	~290-300

The complexity required to adequately digest and absorb nutrients is highlighted in Table 2; this table indicates many intestinal parameters that contribute to gut health and lists the values that clinicians and researchers regard as normal function. The scope of what the gut wall deals with in a day is highlighted by the amount of fluid in the lumen per day, which is 9 liters. Only about 2 liters comes from the diet, the rest is from endogenous secretions that aid in the mixing and digesting of food components. More importantly, only 0.2 liters are lost in the stool per day. Osmolality, pH and peristaltic frequency are factors that will contribute to the physico-chemical environment required for complete digestion of food. Suggestions for measurements to detect deviation from the normal range of these parameters include monitoring barrier function, microbial activity, physico-chemical conditions, enzyme activity in the lumen and brush border, and nutrient absorption (Table 3) (2).

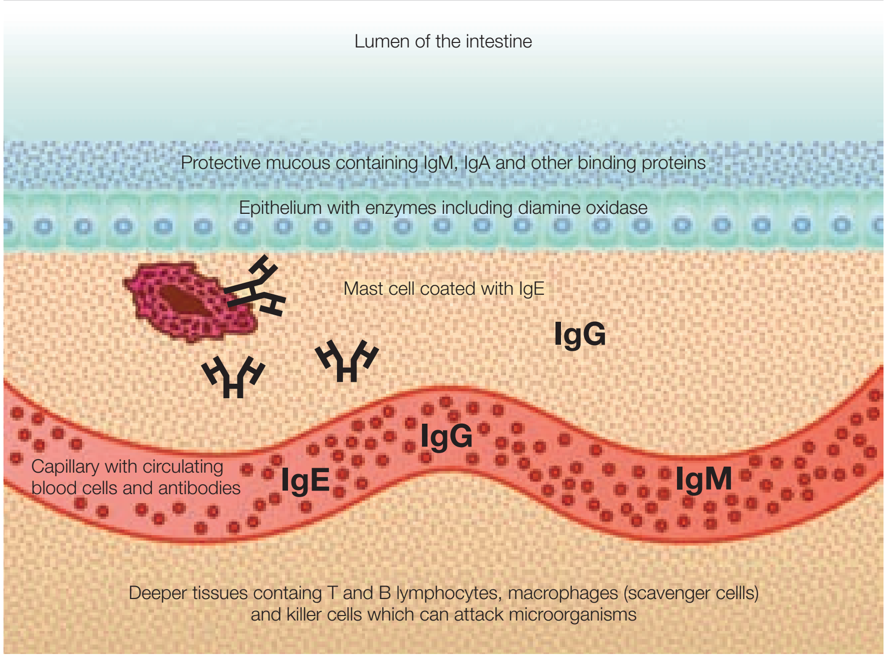
Measuring all of the parameters listed in Table 3 is invasive and expensive. Researchers in the Netherlands have developed the idea of a gut health index which considers a group of factors that contribute to gut health including operation of the functional aspects of nutrient transfer and structural integrity (2). Clinically, lactose malabsorption can be measured by a hydrogen breath test. Permeability can be measured using a test drink of different sugars. Stool samples can be measured for the presence of lipids (25).

This monograph has been divided into the aspects of gut health outlined in Table 3 and each factor has been examined to explore the role of whey protein, lactose and dairy minerals on gut health, including impact on barrier function, microbial activity, physico-chemical conditions, enzyme activity and nutrient absorption based on data from both human and animal models.

Table 3. Gut Health Factor and Measurement

Gut Health Factor	Measurement	Influences
Barrier function	Mucus production Permeability coefficient Epithelial turnover, bile acid secretion, hydrochloric acid secretion and the GALT	Resistance to disease
Microbial activity	ATP Volatile fatty acid conc. (SI) Bile salt conc. Digestion Thickness of GI tract	Immune competence
Physico-chemical conditions	pH Viscosity Retention time	Completeness of digestion
Enzyme activity	Trypsin Chymotrypsin Sucrase Maltase Alkaline phosphatase Glutamyletransferase	Macronutrient digestion
Nutrient absorption	Villus height Crypt height Villus width Enterocytes per villus Enterocytes per um villus	Vitamin and mineral uptake

Figure 2. The Intestinal Wall



Credit: Lessof M.H. 1994. Food allergy, and other adverse reactions to food. *ILSI Europe Concise Monograph Series*. ILSI Europe, Brussels.

BARRIER FUNCTION

Healthy function of the intestine, including enzyme activity, microbial activity, physico-chemical conditions and absorption of nutrients are dependent on barrier function and performance. Failure of the intestinal barrier leads to immune response, metabolic cost and impairment of gut performance.

The intestinal barrier is the main structural defense of the gut and it interacts continuously with the intestinal contents. Cells are joined to adjacent cells by a complex intercellular junction. Within this junctional complex, the tight junction provides the intercellular seal that regulates solute and water transport between the apical and basolateral layers of the intestine and restricts diffusion of nutrients. The dynamic nature of these tight junctions gives rise to an overall feature of the gut, which is permeability. Increased intestinal permeability has been implicated in Crohn's disease, an inflammatory bowel disease, and also under conditions of psychological stress.

The tight junction is influenced by adjacent cell activity, responds readily to the presence of nutrients in the lumen and is influenced by a wide range of intracellular signals (26). Divalent cations, including calcium and magnesium, found in whey minerals may play an important role in regulating tight junction permeability. To maintain function the intestine must respond to the osmolality of the contents by changing the cell volume and tight junction permeability (7).

Many changes occur in the gastrointestinal environment between birth and the first few months of life. The junctional complex and nutrient uptake mechanisms of the intestine are incomplete and vulnerable at birth. They are developed once there is contact between the gut wall and milk; consequently, formula must be carefully formulated to promote the appropriate development, which includes the development of the intestinal bacteria, mechanisms of oral tolerance and increased enzyme activity. The rapid increases in structural integrity of the gut during the first 6 weeks of lactation lead to improved resistance to disease, immunity and nutrient uptake. This is due to the development of oral tolerance, bacterial colonization and mucus secretion. Breast milk induces barrier function better than standard formula up to 6 weeks of age at which stage apparent differences in intestinal resistance dissipate (27). Whey contains many nutrients associated with the development of gut integrity. Whey protein is a good source of amino acids and bioactive peptides that are associated with intestinal adaptation and mucosal repair, including differentiation (5).

A range of amino acids found in whey, including glutamine and cysteine, are implicated in intestinal adaptation and repair (5). Glutamine and cysteine improve intracellular levels of glutathione, a tripeptide that is a potent cellular antioxidant and contributes to reducing tissue damage caused by inflammation and mucosal repair (5, 28). Glutamine is a preferred fuel source for the epithelial cells lining the small intestine as well as being a precursor for glutathione (16) and has been found to improve the recovery rate of burn victims (30). Glutamine is rapidly utilized by tissues during catabolic states, including infants with gastrointestinal dysfunction (31). Glutathione is a marker for differentiation and assists in maintenance of glutamine stores (32).

Low levels of glutathione and glutamine are indicative of metabolic stress and aging, and are linked to immune activation (33). Decreased levels of antioxidants, including glutathione and glutamine, are associated with inflammatory bowel disease (34), and are subsequent to radiation injury (35). Supplementation of glutamine eased inflammation of the gut mucosa in rodent and porcine models after experimental gastrointestinal insult (29, 36); however, other studies exhibit no effect or negative effects (37).

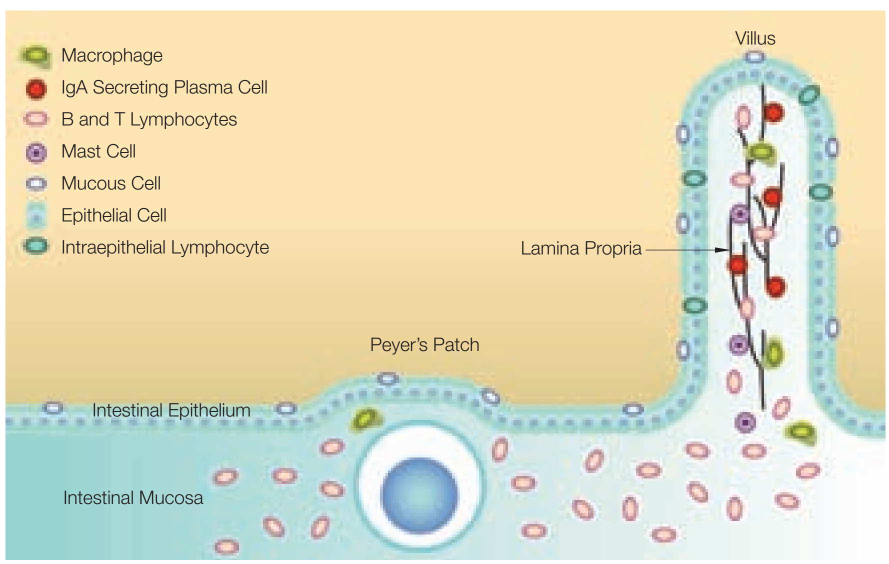
In human studies of Crohn's disease, sufferers consumed diets supplemented with glutamine. The results have been discouraging, perhaps due to the high level of supplementation and exclusion of measures of immune function. While measurement of barrier performance of the intestine is well established in-vivo, data has been found to be more useful when combined with measurement of immune function, particularly in cases of gut dysfunction including Crohn's disease, celiac syndromes or intestinal infections (38).

Definitions

Probiotics are defined as live cultures that when administered in significant quantities confer a benefit to the host. Prebiotics are nutrients or substances that encourage persistence of bacteria by providing substrates for growth.

Supplementation with probiotics and normal enteric microbial population fulfill a role in regulating the barrier function of the intestine. Probiotics modulate paracellular permeability by inhibiting pathogens, may decrease monolayer permeability and stimulate differentiation of the mucosa (39). Incorrect microbial balance by enteropathic E.coli is well documented to cause disruption of tight junction in-vivo (40). Whey contains a number of prebiotic substances that encourage probiotic growth to overcome infection and improve immunity. The importance of stimulating the intestinal lumen by contact with food and bacteria is highlighted in a study of infants transitioning from total parenteral nutrition (nutrients are delivered directly to the circulatory system without contacting the gut). It was shown that enteral nutrition given in small frequent meals exhibited improved immune function and resistance to infection (41).

Figure 3. The Gut Associated Lymphoid Tissue (GALT)



Credit: Saloff-Coste C.J. 1995. Fermented milks: effects on the immune system. *Danone World Newsletter* 9:2-8.

As mentioned earlier, maintenance of the intestinal barrier is critical to health and well being. There are several mechanisms that aid in ensuring the continuity of the epithelial barrier including effective wound healing by cells adjacent to the damage. A specialty whey derivative, insulin-like growth factor I (IGF-1), accelerates intestinal repair and has been demonstrated to aid repair of intestinal tissue for sufferers of bowel disorders including short bowel syndrome, gastric ulceration, intestinal mucositis and inflammatory bowel disease (42). Utilization of IGF-1 has enabled transition from parenteral to enteral nutrition (43).

In addition to its critical relation to the immune system, the intestinal wall is a physical barrier. Permeability of the intestinal epithelium is dependent on the dynamic regulation of the tight junctions. These tight junctions contribute to the ability of creating gradients for nutrients to get into the cell, while preventing the translocation of bacteria across the gut wall into the lamina propria, where they can interact with the immune system and potentially get into the bloodstream. With the villi and microvilli structures in the small intestine, there is an extremely large surface area exposed to the bacteria-filled intestinal lumen. As a result, the gut is the most extensive immunological organ of the body.

MICROBIAL ACTIVITY

Microbial activity in the intestinal lumen has an impact on several different parameters of gut function and the influence on immune competence, as stated in Table 3, depends on the type and balance of bacteria. Immune competence requires that the intestinal wall is able to sense and respond to the bacteria in an appropriate way.

The human intestine is populated by a complex ecosystem of symbiotic nonpathogenic bacteria that have important roles in promoting gut health. The resident bacteria or microflora colonize the colon immediately after birth. The colon has 100 trillion resident bacteria that represent 500-1,000 different bacterial species. This represents the most densely packed ecosystem on earth and also the least diverse; this is because the species that survive the harsh environment of the intestinal lumen have coevolved with humans. This selective pressure has resulted in bacteria carrying out metabolic functions that have not evolved in humans, "arguing" for a truly mutualistic or symbiotic relationship (44).

Colonization of the small intestine is not desirable and relates to a condition called bacterial overgrowth. The intestinal barrier has the dual function of allowing the passage of nutrients while preventing the translocation of bacteria. This leads to the concept of oral tolerance. The gut has a complex system of sampling and cataloguing both food and bacterial antigens and coordinating an immunological hyporesponsiveness to these factors, which the gut is exposed to on a continual basis. However, the intestinal immune system is still able to mount a rapid response to pathogenic bacteria. The immunomodulating effects of whey may relate to this important feature of oral tolerance (45).

From an understanding of the importance of gut bacteria, the field of probiotics has emerged with the aim of reinforcing the intestine from damage by supplying bacteria in the diet that have a range of actions including the secretion of antimicrobial substances, modulating immune response by production of cytokines and influencing metabolic activities (39, 46). The survival and activity of particular strains of probiotic bacteria are challenged by their mode of delivery and the need to survive the harsh acidic environment of the stomach.

Another approach to modulate and improve the bacterial balance in the colon is through the development of dietary components that act as prebiotics. Prebiotics, as noted earlier, encourage the persistence of bacteria by providing substrates for growth. Lactose in whey can be converted to galactooligosaccharides to create a bifidogenic substrate (3).

Prebiotics offer additional benefits to gut health once broken down by bacteria. Bacteria use the prebiotics for growth and in turn increase bioavailable short-chain fatty acids in the colon. These metabolites stimulate proliferation and turnover of intestinal cells. Butyrate, a short-chain fatty acid, is a fuel source for cells in the colon. Various probiotic lactic acid bacteria, including lactobacillus GG and lactobacillus lactis, hydrolyze milk proteins into bioactive peptides. Whey peptides created during digestion (as shown through in-vivo studies) have a variety of potentially beneficial effects including angiotensin converting enzyme (ACE) inhibitory action. Some in-vitro studies have demonstrated opioid-like activity as anti-thrombotics and an ability to reduce cholesterol levels (47).

Whey derivatives or fractions associated with the stimulation of immune function are also available, such as glycomacropeptide, which is associated with immune stimulation, antimicrobial effects and satiety (48-50). Lactoferrin also has some immunomodulatory and antimicrobial effects (51). Partial hydrolysis of whey proteins to smaller bioactive peptides may stimulate the mechanism of oral tolerance that is an important component of overall immune functioning (52).

PHYSICO-CHEMICAL CONDITIONS

A challenge the intestinal wall faces is a harsh and ever changing luminal environment. The physico-chemical properties of pH, viscosity and retention time that were described in Table 3 relate to the proper digestion and delivery of food to the small intestine in such a way as to match nutrient load with absorptive capacity. Therefore, slower digestion and more frequent feeding benefit nutrient uptake in the intestine.

Whey has an unusual digestive profile with rapid gastric emptying and relatively slow intestinal transit time compared to casein (53). Inhibition of gastric emptying is an important feedback mechanism to control the delivery of stomach contents to the intestine and the release of cholecystokinin (CCK). Protein is one of the most satiating foods, but as mentioned earlier, not all proteins are equal in this regard. The whey protein in one study demonstrated increased greater levels of plasma amino acids, CCK and glucagon-like peptide (GLP)-1 and reduced food intake and increased satiety while emptying faster than casein (which coagulates under the acidic conditions of the stomach). The inducement of satiety results in whey being a popular inclusion in weight management formulations (53, 54). Gastrointestinal reflux in children and adults is associated with a slower than normal rate of gastric emptying (55). In a comparison of two different whey-based formulas differing only in their energy density in infants that had volume intolerance and were prone to emesis and gastro-esophageal reflux following feeding were shown to empty at a similar rate. Thus, the whey protein component was able to override the inhibition usually associated with higher energy content, and it allowed these infants to gain weight without the negative gastrointestinal effects (56). Whey added to a liquid meal has been a useful inclusion to the diet of children due to a improved gastric emptying profile compared to energy density and volume (56).

A popular strategy in animal nutrition to slow intestinal transport is to increase meal viscosity since, as a general rule, liquids empty significantly faster than solids (2). Whey protein, whey powder and β-lactoglobulin used as thickeners or emulsifiers in food could be added to formulations to slow intestinal transit time and improve the digestibility and retention time of these foods. A human study examined digestibility of test foods containing 60.4% carbohydrate to which 5.6% low or high viscosity guar gums were added; those containing guar gum had a lower glycemic load and took longer to pass through the duodenum (57). Therefore, there is an opportunity to design and consider these variables in the formulation of new whey products that deliver the benefits of greater retention and absorption.

ENZYME ACTIVITY

The ultimate goal of the gut is processing and absorbing nutrients; food is a complex mixture and nutrients can be inaccessible without adequate and specific enzyme activities that break the intestinal contents down. Digestion of macronutrients is therefore a critical step in the process of nourishing the body. The high level of protein and lactose in whey stimulates the production of enzymes for their hydrolysis. Magnesium acts as a catalyst in many enzymatic reactions and is an important component of dairy minerals.

Enzyme production is influenced by the levels of nutrients present in the diet, and in the case of protein, is proportional to intake and quality (58, 59). Approximately 0.75g/kg/day of good quality, digestible protein is required to provide essential amino acids and positive nitrogen balance in a normal healthy adult (60). Amino acids and di or tripeptides are the absorbable products of protein digestion that can be transported across the epithelium via integral membrane transport proteins.

Whey is an excellent source of bioavailable protein. Whey protein concentrate has the highest biological value of all proteins and has higher PER and NPU than soy protein, cow's milk, casein or beef (9). This unique profile promotes uptake of all the essential and non-essential amino acids that are desirable for optimal health.

The high PER of whey is due to the presence of high levels of branched amino acids: isoleucine, leucine and valine, and the sulphur-containing cysteine and methionine (9). In a protein-replete diet, these amino acids support the uptake and formation of non-essential amino acids including glutamine and glutathione. Glutamine and glutathione are also beneficial to other aspects of gut health, particularly in times of metabolic stress.

The cells of the brush border act as a nutrient reservoir during catabolic periods. During 24 hour fasting, malnutrition, famine and disease, intestinal mass can decrease, leading to rationalization of energy costs of respiration, although the situation is rapidly reversed on feeding with high quality protein (61).

Nutrient uptake mechanisms, particularly enzyme production, decrease during malnutrition and famine. Low levels of protein intake result in increased uptake of essential but not non-essential amino acids associated with gut health (5). Normal levels of amino acid uptake return in proportion to availability when protein intake is increased.

During gastrointestinal illness elevated cell turnover or increased loss of plasma protein of the gastrointestinal tract can be expected, increasing normal energy, protein and amino acid requirements (2, 62).

Dairy products and whey contain appreciable levels of lactose. Whey solids contain approximately 70% lactose, but whey products containing high levels of proteins (such as whey protein isolate and whey protein concentrate 80%) contain lower amounts. Please contact your U.S. whey supplier or consult USDEC's technical materials for additional information on lactose content. With few exceptions, lactose is the principal carbohydrate source in all mammalian milks and is readily consumed by newborn infants. The enzyme associated with the transport of glucose and galactose, from lactose, across the brush border membrane is the sodium glucose linked cotransporter and is abundant along the length of the small intestine (6). The lactase enzyme is a β-galactosidase responsible for hydrolysis of lactose, and its expression is limited in the majority of the world's population. Persistence of the enzymatic activity is dependent upon the continuing levels of lactose in the diet and on gastrointestinal health (63) and the ethnic background of individuals (persistence occurs for most Caucasians and some isolated tribes from Africa). Some genetic factors may also be involved (64). Adaptation can be achieved in some individuals by slowly increasing their lactose consumption over their threshold (65). Small amounts of lactose (up to 12 g/day) consumed with meals are generally well tolerated even in lactase non-persistent adults. In these conditions, lactose can act as a prebiotic.

Lactose has a lower glycemic index than glucose because of the time required for digestion and the limited specific β-galactosidase enzymatic activity, which results in longer retention time in the gut and slower absorption across the gut wall.

NUTRIENT ABSORPTION

In the gut health factors listed in Table 3, the primary factor contributing to nutrient absorption is the surface area, which is measured by crypt and villus height and the number of enterocytes along the crypt-villus axis (2). The proposed influence on gut health relates to the improved vitamin and mineral uptake. In general, the uptake of both macro and micronutrients is an important indicator of intestinal health and a reflection of the overall intestinal efficiency.

Dairy products and whey are sources of bioavailable nutrients, which contribute to the efficiency of their absorption and have been shown to promote absorption of other dietary nutrients. Numerous compounds in whey produce these effects, with more to be discovered in the future (3). Since the very first nutritional studies, it is well understood that nutrient absorption and bioavailability can vary substantially between individuals and treatments. In most studies, dairy products persist as the most bioavailable dietary source of nutrients regardless of individual variation within groups, perhaps due to universal enhancement of gut functioning.

Studies indicate that intake of whey protein enhances vitamin and antioxidant uptake, leading to enhanced immune function (66). Antioxidants are associated with decreasing risks of developing degenerative processes, such as some kinds of cancer, cardiovascular and neurodegenerative diseases, and age-related macular degeneration. Also, improved cell-to-cell gap junction communication is observed in tissues high in antioxidants.

Milk has been demonstrated to significantly enhance intestinal uptake of this important nutrient. In a 4 day rotation study, folate uptake measured by erythrocyte folate and plasma tHcy concentration, but not plasma folate concentration, was enhanced by milk consumption in a group of 31 young women (67).

Whey products contain lactoferrin, which is also available as an ingredient (iron-saturated or not) from U.S. suppliers. Lactoferrin is an iron binding peptide that has been shown to enhance dietary iron uptake in Caco-2 cells, a model system often used for intestinal absorption studies. Lactoferrin (in its iron-saturated form) is useful in the treatment of anemia (68), but its role as an antibacterial agent is more developed.

It is well established that lactose enhances in-vivo uptake of calcium and magnesium from infant formula (69), calcium uptake in rat studies (70) and zinc in piglets (71). Simple cell in-vitro models have also demonstrated that lactose enhances calcium and magnesium uptake (72). Whey and dairy minerals tend to be more bioavailable than equivalent non-dairy sources. An in-vitro study suggests the enhanced bioavailability is due to the unique mineral composition of milk that causes stimulation of cell activity and regulation of intercellular junctions (72). Furthermore, it is well known that lactose enhances the paracellular component of the intestinal calcium transport system and not the vitamin D-dependent active transcellular component.

CONCLUSION

The gastrointestinal tract is a highly specialized and complex organ that remains of great interest to researchers in a broad range of disciplines. Much work is still to be done to elucidate, characterize and validate all of the benefits of whey on gut health.

In this monograph, whey and its derivatives are examined to evaluate their contribution to the healthy functioning of the gastrointestinal tract. Whey and whey derivatives have been demonstrated as useful dietary components for the maintenance of gut health and in the treatment and prevention of disease. Whey products are a useful dietary component to assist in nutrition of those that are susceptible to or suffering from disease, the young, athletes or those interested in improving their general health.

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