3

The Impact of Probiotics on the Gastrointestinal Physiology

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1. Introduction

Researches concerning probiotics were initiated by a Russian scientist named Elie Metchnikoff. He emphasized the importance of *Lactobacillus* species and fermented milk products present in the gastrointestinal tract for a healthy and long life. The term "probiotics" was first introduced in 1953 by Werner Kollath, and he defined probiotics as microbially derived factors that stimulate the growth of other microorganisms. Afterwards, the term "probiotics" was defined by Roy Fuller in 1989 as a live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance. Fuller's definition emphasizes the requirement of viability for probiotics and introduces the aspect of a beneficial effect on the host. Although, this definition has been widely used by the entire scientific world, according to the currently adopted definition by FAO/WHO, probiotics are: "Live microorganisms confer a health benefit on the host when administered in adequate amounts" (FAO/WHO, 2001).

The most frequently used probiotic microorganisms are Lactobacillus and Bifidobacterium species. However, there are also much more bacteria and some yeast species used as probiotic. Bacteria and yeast species, which are used commonly as probiotic, are listed by Heyman & Menard (2002) as below. *Lactobacillus* species: *L. acidophilus, L. rhamnosus, L. gasseri, L. reuteri, L. bulgaricus, L plantarum, L. johnsonii, L. paracasei, L. casei, L. salivarius, L. lactis. Bifidobacterium* species: *B. bifidum, B. longum, B. breve, B. infantis, B. lactis, B. adolescentis.* Other species: *Streptococcus thermophilus, Escherichia coli, Bacillus cereus, Clostridium butyricum, Enterococcus faecalis, Enterococcus faecium.* Yeast: *Saccharomyces boulardii, Saccharomyces cerevisiae*, VSL#3 (four strains of lactobacilli, three strains of bifidobacteria, one strain of *Streptococcus salivarius* sp. *thermophilus*).

There is a mutual interaction between intestinal cells and microorganisms present in the gastrointestinal tract. Commensal microorganisms in the gastrointestinal tract have multidirectional effects on digestion, absorption and barrier function, secretory functions, or postnatal maturation of intestinal mucosa. Furthermore, it has been known that they change gene expression in intestinal cells (Hooper et al., 2001). The changes in the function of intestinal tract (e.g. the increase of motility, or disruption of carbohydrate digestion) also affect bacteria population and colonization.

Probiotics are widely used for the promotion and improvement of health in humans and in animal species. Probiotics have been used as a biologically active substance in a large extend of pathologic conditions ranging from antibiotic-associated or travelers' diarrhea, irritable bowel syndrome (IBS), and lactose intolerance to dental caries, ulcers due to *Helicobacter pylori,* hepatic encephalopathy, intestinal motility disorders and neonatal necrotizing enterocolitis (Deshpande et al., 2011). It has been used as a growth, or production performance promoter in poultry species or farm animals. There are also numerous scientific reports about the interaction between probiotics and immune system. On the other hand, the effects of probiotics on digestive physiology and intestinal tract morphology have not been documented sufficiently. Therefore, the objective of this chapter is to assess the effects of probiotics on gastrointestinal physiology and morphology in human and animal models. The effects of probiotics on digestive and absorptive function of the intestine, expression of brush border enzymes and nutrient transport systems have been investigated in this chapter. The relationship between probiotics and gut motility or transit time of gastrointestinal content has also been highlighted. The effects of probiotics on morphological characteristics and the proliferation capacity of crypt and villus epithelium have been focused and in addition, the effects of probiotic on enteric nervous system have been evaluated. Finally, impact of the probiotics on the physical and functional barrier of gastrointestinal tract has been evaluated in this chapter.

2. The effects of probiotics on intestinal morphology and cell proliferation

To investigate the effects of microorganisms on the development of digestive tract, generally animal models are used. Because, obtaining and examining intestinal mucosal samples of people are technically more difficult. The morphological parameters such as length of villi, depth of crypt, villi/crypt proportion, and surface area of villi are used to investigate the effects of microorganisms on intestinal morphology and cell proliferation. The height of villi and the depth of crypt are considered as the indicators of intestinal functions.

In the comparative studies conducted on germ free and conventional animals it has been determined that microorganisms located to digestive tract during the postnatal period caused to decreased villi length and increased crypt depth in conventional animals i.e. in pig (Willing & Van Kessel, 2007), in rat (Ishikawa et al., 1999) and in birds (Furuse & Okumura, 1994). However, it has been also reported that there is no difference between germ-free and conventional animals regarding development of villi (Sharma et al., 1995). It has been determined that length of villi is higher in gnotobiotic animal models as in germ-free animals compared to conventional animals (Herich et al., 2004). The effects of probiotics have been investigated by inoculating probiotics to germ free animals or supplementing conventional animals with probiotics.

2.1 Villus height

Willing & Van Kessel (2007) have reported that villus height was increased in gnotobiotic piglets inoculated *Lactobacillus fermentum* (monoassociated with *Lactobacillus fermentum*) and Di Giancamillo et al. (2008) also has reported increase in villus height in piglets supplemented with *Pediococcus acidilactici*. Yang et al. (2009) have investigated intestinal tract morphology of mice supplemented orally high, low and moderate doses of *Bifidobacterium adolescentis* BBMN23 and *Bifidobacterium adolescentis* BBMN68 after 2 and 4

weeks of application. Villus height was longer in low dose group compared to those of controls, but moderate and high doses did not affect it after two weeks. However after 4 weeks, villus height increased in all groups supplemented with probiotic. Similarly villus height increase has been reported in studies conducted on birds as an animal model (Samli et al., 2007; Awad et al., 2010).

Effects of the probiotic on villus height may change depending on the species of microorganism or probiotic. For example, villus height in duodenum and ileum increased but did not changed in jejunum of broiler chicks supplemented with *Pediococcus acidlactici* as probiotic (Taheri et al., 2010). On the other hand Günal et al. (2006) reported that villus height of jejunum and ileum increased in broiler chicks applied multi-microbe probiotic product. Segmental differences were also found in comparative studies conducted on germ free and conventional animals. Shirkey et al. (2006) have reported that villus height was the longest in jejunum of pigs supplemented with *Lactobacillus fermentum*. On the other hand Shurson et al. (1990) reported that germ-free pigs had longer ileal and duodenal villi, but shorter jejunal villi compared with their conventional counterparts. *Saccharomyces boulardii* is one of the yeast that has been using as probiotic. It has been determined that there was no significance change in villus height or crypt depth of intestinal biopsy samples obtained from volunteers who were supplemented with *Saccharomyces boulardii* for 14 days (Buts et al., 2002). However, another yeast species (*Saccharomyces cerevisiae*) was reported to increased villus height of ileum in birds (Zhang et al., 2005). Meslin and Sacquet (1984) who investigated microvilli on the surface of enterocytes reported that the microvilli were significantly shorter in all small intestinal regions when the micro flora was present. The decrease in microvillus length (due to the presence of micro flora) in germ free rat, was 5% in the duodenum, 9% in the jejunum and 18% in the ileum. Because increased villus height leads to increased surface area at the same time, digestion and absorption of disaccharides and dipeptides are promoted. In addition, it was indicated that longer villi are correlated with activation of cell mitosis (Samanya & Yamauchy, 2002).

2.2 Crypt depth

The data related to effects of probiotics on crypt depth are inconsistent. Probably there are variations depending on the species, the dose or the application of used probiotic. Yang et al. (2009) have reported that crypt depth decreased in mice supplemented with moderate and high doses of probiotic (*Bifidobacterium adolescentis* BBMN23) for 2 weeks, but on the contrary it was increased in low dose probiotic supplemented group compared to controls. However after 4 weeks of application, increased crypt depth has been reported in moderate and high doses groups. Willing & Van Kessel (2007) have reported that crypt depth was increased in piglets inoculated with *Lactobacillus fermentum* (monoassociated with *Lactobacillus fermentum*) compared to conventional animals. Similarly, increased crypt depth in duodenum, jejunum and ileum of chicks supplemented with *Bacillus subtilis* has been found (Pelicano et al., 2005).

Scharek et al. (2005) have reported that there was no significant change in the crypt depth in proximal jejunum of pigs supplemented with *Enterococcus faecium* 68. Similarly, it has been stated that crypt depth didn't change in duodenum, but decreased in ileum of broiler chicks supplemented with *Lactobacillus sp* (Awad et al., 2009). In addition, it has been reported that crypt depth was not changed in broiler chicks supplemented with *Saccharomyces cerevisiae*

yeast (Zhang et al., 2005). Increased crypt depth indicates that both mucosal secretion (Chiou et al., 1996) and cell turnover are high (Yason et al., 1987).

2.3 Villus height/crypt depth ratio

In studies conducted on germ free animals it has been determined that the villus height/crypt depth ratio is higher in germ free animals than conventional animals (Heneghan et al., 1984). Awad et al. (2010) have reported that villus height to crypt depth ratio increased in duodenum and ileum of chicks supplemented with *Lactobacillus* sp. Similarly, supplementation of multi-microbe probiotic product has been reported to cause increased villus height to crypt depth ratio in duodenum and ileum (Kim et al., 2011). It has been indicated that, increased villus height to crypt depth ratio are directly correlated with an increased epithelial turnover (Fan et al., 1997). Therefore, it may be concluded that bacteria used as probiotic positively affect development of intestinal epithelia.

2.4 Villus surface area

The effects of probiotics on villus surface area may change depending on the segment which bacteria colonized. For example, jejunum villus surface area increased, but duodenum or ileum surface area did not affected in chicks supplemented with probiotic containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Enterococcus faecium* species (Smirnov et al., 2005). Similarly Samanya and Yamauchy (2002) have reported that *Bacillus subtilis natto* increased villus surface dose dependently but this increase varied between different segments. Increased surface area allows for increased intestinal absorptive area. Increased absorptive area is useful because digested nutrients pass into the villi through diffusion, so effectiveness of diffusion increases.

2.5 Cell proliferation, migration and turnover

Proliferation, migration, number and apoptosis of cells in intestinal tract are affected by secreted molecules or fermented products of microorganisms in digestive tract.

It has been determined that cell count and mitotic index in intestinal villus and crypt was higher in gnotobiotic rats mono-associated with *Lactobacillus rhamnousus* GG compared to germ-free or conventional animals (Banasaz et al., 2002). Probiotics both increase cells in intestinal mucosa and affect the migration of cells in crypt to the tip of villus. Canonici et al. (2011) have revealed by *in vitro* and *in vivo* studies that *Saccharomyces boulardii* accelerates migration of intestinal enterocytes through crypt-villus axis by activating α2β1 integrin collagen receptor. Because of this effect, *Saccharomyces boulardii* accelerates the repair of intestinal epithelium damage.

Results related to the effects of probiotics on the proliferation of intestinal epithelium cells are controversial. Mogilner et al. (2007) have reported that *Lactobacillus* GG' did not affect proliferation of enterocytes in rats with short bowel syndrome. Similarly, it has been reported that *Saccharomyces boulardii* did not affect proliferation of enterocytes (Canonici et al., 2011). However Ichikawa et al. (1999) have suggested that *Clostridium butyricum* and *Lactobacillus casei* had tropic effect on digestive tract by enhancing proliferation of intestinal epithelial cells. It has been reported that probiotics increased the production of short-chain

fatty acids (SCFA) (Sakata et al., 1999). Investigators have suggested that proliferative effects of probiotics on intestinal epithelial cells are based on the probiotic induced increased SCFA production. In the same way, Di Giancamillo et al. (2008) have reported that enterocyte proliferation increased in piglets supplemented with *Pediococcus acidilactici*.

Mogilner et al. (2007) have reported that there was a decrease in enterocyte death via apoptosis in rats with short bowel syndrome supplemented with *Lactobacillus* GG.

It has been suggested that bacteria used as probiotic affect functions and counts of the goblet cells in intestinal mucosa other than enterocytes. Because the mucus secreted by goblet cells is one of the factors composing intestinal barrier, it has significance on the prevention of pathogen invasion in digestive tract.

Gauffin Cano et al. (2002) reported an increase in the number of goblet cells after the administration of the probiotic strain *Lactobacillus casei* CRL 431 in a malnourished mouse model. In addition there is ample evidence that intestinal microbiota affect goblet cell dynamics, including mucus secretion and composition either directly by the secretion of bioactive factors or indirectly by the activation of host immune cells (Sharma et al., 1995).

3. The effect of probiotics on the motility of the gastrointestinal tract

Either gastrointestinal motility or the kinetic of its content is one of the most important variations providing gastrointestinal tract's comfort. The changes in motility can make symptoms varying from constipation to diarrhea come into being (Ohashi & Ushida, 2009). The interest to probiotics, due to their motility regulatory effects, is rising in functional gastrointestinal disorders.

The influence of microorganisms on intestinal motility was reported for the first time by Abraham and Bishop. These researchers observed that both small and large intestinal transit time and gastric emptying decreased in germ-free animals (Abraham & Bishop, 1967). Husebye et al. (1994) detected that phase-3 intervals in migrating motor complex (MMC) in germ-free animals were extended. In addition, they noticed that the motility became normal when specific pathogen free bacteria were inoculated in these animals' intestines. They also noticed that the motility of intestines became normal when probiotics were inoculated instead of doing so with commensal bacteria.

Actually gastrointestinal motility and microorganisms in the tracts are mutually influencing each other. The presence or the absence of the motility affects microorganisms' colonization and also the motility is being altered in case the microorganisms are lacking. Both migrating motor complex in stomach and the one way peristaltic movements in small intestine influence the colonization in the area (Quigley, 2011). Thus the decrease of intestinal motility causes small intestinal bacterial overgrowth (SIBO).

In addition to commensal bacteria in gastrointestinal tract, those used as probiotic were also detected to be influencing the motility (Williams et al., 2010). Diverse researches related to the subject in both human and animal models were conducted. Massi et al. (2006), observed *in vitro* the influence of probiotics on motility in ileum and proximal colon segments isolated from guinea pigs. They realized that *Lactobacillus* and cytoplasmic extract obtained from *Bifidobacterium* caused a contraction in ileum and a relaxation in proximal colon. They claimed that the extract mentioned above does not exert its effect via muscarinic receptors

since its effect was not inhibited by atropine. Yet, its mechanism is not fully elucidated so far (Waller et al., 2011).

The motility-probiotic relationship in humans was both in healthy individuals and in case of different diseases evaluated despite of technical difficulties. Indrio et al. (2008) who observed the connection between gastric emptying and the probiotics determined that gastric emptying time in infants being given *Lactobacillus reuteri* was significantly rapid compared to those in placebo group. Cherbut et al. (1997) noticed that the motility of terminal colon rises while sleeping in humans supplemented with *Lactobacillus casei*. Marteau et al. (2002) reported *Bifidobacterium lactus* strain DN 173010 to reduce colonic transit time in healthy female individuals. Waller et al. (2011) explained that whole gut transit time (WGTT) decreased in a dose-dependent manner in male and females obtaining different doses of *Bifidobacterium lactis* HN019 during 14 days.

Indrio et al. (2009) observing electrical activity that forms motility reported that the percentage of propagation (the electric activity turning into peristaltic movement) was higher in infants to which *Lactobacillus reuteri* was given compared to those in placebo group.

Lots of diseases such as irritable bowel syndrome (IBS) causing gastrointestinal dysfunction, also influence digestive tract motility or its motor activity. Probiotics are used in treatment of motoric function disorders seen in such diseases' post infective periods. For example post infective period hyper contractility was observed to be present in digestive tract of mice infected with *Trchinella spiralis*. It has been observed that the hyper contractility in mice given *Lactobacillus paracasei* NCC2461 specifically weakened (Verdu et al., 2004). In the same way delayed gastric emptying was observed in mice infected via *Helicobacter pylori*. Gastric functions were detected to be normalized in the same mice following probiotic treatment with *Lactobacillus rhamnosus* R0011 and *Lactobacillus helvaticus* R0052 (Verdu et al., 2008). Agrawal et al. (2009) reported that both colonic and orocecal transit were accelerated when fermented milk product containing *Bifidobactreium lactis* DN-173010 were given to patients suffering from irritable bowel syndrome presented with abdominal distension and constipation and also that this was making the case symptoms' influences to be diminished. Intestinal transit time was detected to be lengthened in diseases representing with digestive tract functional disorders such as IBS. Even the mechanism that lies beneath is not fully elucidated; it was estimated to be related to the imbalance in intestinal micro flora due to the illness itself.

The effects of probiotics on intestinal tract are being influenced by diverse factors. The motility in intestinal tract was acclaimed to be possibly specific to the type of the probiotic used (Husebye et al., 2001). Either the physiologic situation of the human or the animal is another factor affecting the motility. For example it was detected that in elderly people, *Bifidobacterium* DN 173010 reduces oro-fecal transit time while the same bacteria accelerates only colonic transit time in healthy volunteers. In addition, its effects in males were established to differ from that in females (Meance et al., 2001).

3.1 The mechanism of action

The mechanism lying beneath the effects of probiotics on motility are not fully elucidated. Yet the probable influence mechanisms can be divided into three headlines; 1) Products

secreted by bacteria or final products formed at the end of fermentation 2) Influence of microorganisms on intestinal neuroendocrine factors 3) Influence of mediators secreted due to gastrointestinal tract's immune reaction (Barbara et al., 2005).

The stimulation of colonic motility via the rise of fecal bacterial mass, the stimulated cholecystokinin and deconjugated or dehydroxylated bile salts is considered to be a part of other mechanisms. Some probiotics such as *Bifidiobacteium lactis* HN019 stimulate the production of lactic acid bacteria in the environment. As a consequence of lactic acid bacteria production, WGTT time decreases while peristaltic accelerates owing to the reduction of the intestinal content pH (Salminen et al., 1997).

A high number of gas occurring due to the digestion of indigested carbohydrates by colonic microbiota influences intestinal motility. Yet different influences may occur in motility related to the gas type formed. For example, when methane producing bacteria in intestinal flora multiplies, compared to the effects of those releasing hydrogen, intestinal transit time increases, motor activity is directly inhibited, and on the contrary non propulsive and segmental contractions increase (Pimentel et al., 2006).

Short chain fatty acid (SCFA) appearing as an outcome of carbohydrate or lipid fermentation by probiotics is one of the most important final products influencing gastrointestinal motility. Cherbut et al. (1997) observing the influence of SCFA on motility detected that SCFA showed contractile activity via enteric cholinergic reflex in low concentrations (0.1 to 10 mmol/L). Nevertheless this was also detected to be a temporary effect. SCFA in high concentrations (100 mmol/L) was observed to inhibit colonic contraction (Sakata, 1987). McManus et al. (2002) reported that SCFA inhibits peristaltic activity while it stimulates the tonic activity in the large intestine of dogs. It exerts this effect by influencing Ca^{+2} influx to gastrointestinal smooth muscle cells. Besides colonic motility SCFA was also determined to influence upper part of digestive tract, to cause relaxation in both lower esophageal sphincter and proximal stomach and also it decreases gastric emptying time. It was explained that it showed this effect via hormonal way with the use of polypeptide YY (Labayen et al., 2001).

In addition, probiotics affect the motility in an indirect way by influencing some inflammatory mediators' expression occurring during the disease that alters gastrointestinal tract functions. For example, *Lactobacillus paracasei* weaken the hyper contractility rising in the post infective period of diseases by increasing the expression of COX-2 being one of the inflammatory mediators (Verdu et al., 2004). Mediators such as TGF-β and prostaglandin E(2) released during gastrointestinal diseases damage both enteric nervous system and interstitial cells of cajal. Disorders in the motility occur since the neuronal structures mentioned above regulate intestinal tract motility. Probiotics given in post infective period normalize the motility as they accelerate the healing of damaged cells in enteric nervous system (Indrio et al., 2008).

4. Effects of probiotics on pancreatic digestive enzymes

There is only limited research on the effects of probiotics on pancreatic digestive enzymes such as amylase, lipase, trypsin, chymotrypsin, although there are few publication related to effects of probiotics on mucosal digestive enzymes. The relation between microorganisms of intestinal tract and pancreatic enzymes has been investigated in some studies using germ-

free animals. It has been indicated that the bacterial status altered preferentially the exocrine pancreatic function. The specific activities of amylase, trypsin and carboxypeptidase-A were lower in germ-free than in conventional rats (Lhoste et al., 1996). How microorganisms in digestive tract affect secretion of pancreatic enzymes has not been determined. However hormones which stimulate enzyme secretion in pancreas such as enteroglucagon, gastrin or pancreatic polypeptide have been reported to be lower in germ-free animals compared to conventional animals (Goodlad et al., 1989). Decreased pancreatic enzymes in germ-free animals may be explained by this report. Moreover the cecal micro flora may also affect the pancreas via its metabolites. In fact, SCFA can stimulate amylase release from the rat pancreas directly (Ohbo et al., 1996).

Matur et al. (2007) have been reported that chymotrypsin levels decreased but amylase, lipase and trypsin levels did not changed in pancreas of broiler chicks which were supplemented with *Enterrococcius facium* NCIMB10415. In addition, intestinal tract enzyme activities were reported to be lower in animals supplemented with probiotics than those of control animals in the same study. The researchers have suggested that the relevant probiotics may affect the biosynthesis of pancreatic enzymes or their secretion to small intestines, although the mechanism underlying this effect has not been fully elucidated yet.

Microorganisms in digestive tract may also affect digestive enzyme activities indirectly. Drouault et al. (2002) have reported that *Lactobacillus lactis* produces lipase and this lipase ameliorated steatorrhea in pigs fed on high lipid meal.

4.1 Probiotic application in diseases related to digestive enzyme deficiencies

Sucrase deficiency, also known as sucrase-isomaltase deficiency, is the most common disaccharidase deficiency in human. It is a genetic disorder and causes to malabsorption of sucrose in diet and consequently to accumulation of hydrogen in the colon, swelling, diarrhea and abdominal cramps (Rolfe, 2000). *Saccharomyces cerevisiae* expresses significant sucrase and some isomaltase activity, and it has been proposed to improve malabsorption in patients with sucrase-isomaltase deficiency (Harms et al., 1987). Similarly Treem et al. (1993) have reported that the liquid preparation which is a by-product of the manufacture of baker's yeast reduced breath hydrogen excretion in patients with congenital sucrase-isomaltase deficiency that were given a sucrose load and allowed most patients to consume a sucrose-containing diet.

4.2 Lactase deficiency

Lactase insufficiency means that the concentration of the lactose cleaving enzyme β-galactosidase, also called lactase, in the brush border membrane of the mucosa of the small intestine is too small. Lactase deficiency is a very common condition characterized with lactose malabsorption in the intestinal mucosa. High concentrations of lactase enzyme are physiologically present in neonates. In the post weaning period, an irreversible reduction of its activity occurs in human (Montalto et al., 2006), and in mammalian animal species (Batchelor et al., 2011). Secondary lactase deficiency can be seen any condition that damages the small intestinal epithelial cells or significantly increases the gastrointestinal transit time. Thus, secondary hypolactasia is transient and reversible (Montalto et al., 2006).

It has been observed that patients with lactose maldigestion had higher lactose tolerance when eating fermented dairy products such as yogurt and could easily digest them compared to milk. There are two mechanisms lying beneath this situation. First, β-galactosidase is released from bacteria in yogurt after digested by bile acids. Second, delaying gastric emptying and slowing intestinal transit times prolong the action of residual β-galactosidase in the small intestine and decrease the osmotic load of the lactose (Marteau et al., 2001). Ojetti et al. (2010) were investigated hydrogen breath excretion and gastrointestinal symptoms as indicators of lactose intolerance in patients. They have reported that hydrogen excretion decreased and clinical symptoms improved in the group given *Lactobacillus reuteri* compared to those of placebo group. De Vrese et al. (2001) tested whether live bacteria in the fermented or non-fermented milk product are a prerequisite for enhanced lactose cleavage by microbial β-galactosidase. They found that lactose digestion in lactose malabsorbers and gastrointestinal well-being can be significantly improved if a milk product contains active microbial β-galactosidase. The bacteria need not to be alive but intact cell walls are required to act as a mechanical protection of the enzyme during gastric passage.

5. The effect of probiotics on the absorptive function of the intestine

5.1 Sodium and chloride absorptions

It has been determined that two carrier proteins play a role in the sodium absorption; "sodium hydrogen exchanger-2" (NHE-2) and NHE-3 which are the members of "solute carrier family-9" (SLC9) (Malakooti et al., 2011). While NHE-2 is expressed mostly in colon, NHE-3 is expressed mainly in ileum (Dudeja et al., 1996). The carrier proteins "down regulated in adenoma" (DRA) and putative anion transporter-1 (PAT-1) from SLC26 gene family have a role in chloride absorption. While PAT-1 is mainly expressed in small intestines, DRA is more expressed in colon than small intestines (Wang et al., 2002).

Probiotics such as *Lactobacillus* are used as a treatment support in diseases especially characterized by fluid loss in children. It has been determined that probiotics reduce sodium chloride and fluid loss in these diseases (Raheja et al., 2010). Furthermore it has been reported that *Saccharomyces boulardii* increases chloride net absorption from jejunum and descending colon *in vitro* (Krammer & Karbash, 1993).

To investigate the molecular mechanisms underlying the effects of probiotics on electrolyte and water absorption from intestinal tract, some *in vivo* and *in vitro* studies have been carried on. Human colon adenocarcinoma cell (Caco-2) has been used extensively as a model cell *in vitro* experiments subjected intestinal epithelium. Borthakur et al. (2008) reported that DRA activity increased in Caco-2 cells after short term *Lactobacillus acidophilus* application and this will cause chloride absorption eventually. *Lactobacillus acidophilus* was reported to cause this effect by increasing DRA expression in apical membranes of epithelial cells. However, it has been determined that total DRA amount in the cell did not changed, only DRA expression on the surface increased and this effect was caused via phosphatidyl-inositol 3-kinase pathway. It has been also considered that some soluble substances secreted by *Lactobacillus acidophilus* revealed this effect.

Bacteria present in the intestines are consistently interacting with epithelial cells. Therefore, it has been determined that, while *Lactobacillus acidophilus* increase DRA mRNA expression

in epithelial cells of colon by transcriptional mechanisms, it is not effective in jejunum and ileum during its long-term applications. DRA is primary chloride transporter in colon, therefore significance of probiotics in chloride and water absorption has been proved (Binder & Mehta, 1989; Raheja et al., 2009). There is a limited knowledge on the molecular mechanisms underlying the effects of probiotics on sodium absorption. It is well known that probiotics produce short chain fatty acids. The short chain fatty acids increase the expression of NHE-3 which plays a main role in the absorption of sodium from ileum (Kiela et al., 2007).

5.2 Na^+-coupled glucose absorption

Glucose is absorbed from intestinal brush border membrane by mainly sodium-dependent glucose co-transporters 1 (SGLT-1) and glucose transporter 2 (GLUT-2) (Shimizu et al., 2000). Absorption rate of the intestinal glucose depends on the SGLT-1 affinity and density in the membrane. High affinity SGLT-1 is primary transporter for glucose absorption.

It has been reported that sodium coupled glucose absorption increased in small intestines of pigs treated with *Saccharomyces boulardii* or *Bacillus cereus var. toyoi* (Breves et al., 2000). It has been also determined that *Enterococcus faecium* NCIMB 10415 used as a probiotic caused an increase in intestinal transport and barrier function and glucose absorption (Lodeman et al., 2006). Similarly, sodium coupled D-glucose absorption increase has been reported in rats orally applied *Saccharomyces boulardii* (Buts et al., 1999).

The mechanism underlying the sodium coupled glucose absorption increasing effect of probiotics in intestinal epithelium cells has not been fully defined. However it has been suggested that specific and non-specific mechanisms may be effective. It may be a non-specific reason such as an increase in the absorptive surface or in affinity of transporters to substrates due to probiotics. On the other hand Rooj et al. (2010) have reported that supernatant obtained from lactobacilli increased the glucose transport in Caco-2 cells non-genomically and undefined metabolites produced by the probiotic caused this effect. This researchers have suggested that the metabolites produced by the probiotic cause to expression of cytosolic transporters in brush border membranes of enterocytes or to activation of transporters which were already in the membrane.

Although it has been suggested that probiotics affect intestinal glucose transport by non-genomic responses, SGLT-1 expression increases in rats applied *Saccharomyces boulardii* (Buts, 2009). Therefore, it is considered that the probiotics may be effective by changing gene expression via transcriptional or post translational mechanisms.

5.3 Calcium absorption

It has been reported that probiotics increase the calcium absorption from intestinal tract. However mechanisms underlying the increasing absorption are not fully elucidated and more than one mechanism may be considered (Gilman et al., 2006). Fermentation products occurred as a result of probiotics' activity may increase the absorption surface by accelerating proliferation in enterocytes (Scholz-Ahrens at al., 2007). Furthermore short chained fatty acids and the other products produced by the bacteria decrease the pH of intestines microenvironment. Therefore, calcium solubility increases and this may be related to increased calcium absorption (Gilman et al., 2006; Scholz-Ahrens at al., 2007). Tang et al.

(2007) reported that fermenting calcium-fortified soymilk with some *Lactobacillus* species can potentially enhance the calcium bioavailability.

Brassart & Yey (1998) have determined that 7 *Lactobacillus* species, which were tested *in vitro*, increased the transepithelial calcium transport in Caco-2 monolayer cells. Gilman & Cashman (2006) have reported that the transepithelial calcium transport did not change in Caco-2 monolayer cells treated by *Lactobacillus salivatorius* (UCC 118) and *Bifidobacterium infantis* (UCC 35624), however UCC 118 increased calcium uptake after 24 hours. Although the differences between the results of these studies have not exactly clarified, it has been suggested that the differences may be due to the different adheration of used bacteria to epithelial cells (Gilman & Cashman, 2006). Intestinal calcium absorption increasing effect of probiotics may be also related to increased expression of calcium channels in intestinal mucosa. Vinderola et al. (2007) observed that supernatant from milk fermented by *Lactobacillus helveticus* R389 enhanced expression of TRPV6 channels in the duodenum. Enhanced expression Ca^{+2} channels indicate an improved capacity for dietary Ca^{+2} uptake.

5.4 The effects of probiotics on cholesterol absorption

Cholesterol entered the body via food or re-absorbed from the bile secretion to the blood, is primary factor for heart and vascular diseases. Hypercholesterolemia is one of the most significant risk factor for the cardio-vascular diseases. It has been determined that various probiotic species decrease the serum cholesterol levels in human (Larkin et al., 2009), experimental animals (Park et al., 2007) or farm animals (Özcan et al., 2003; Strompfova et al., 2006). However hypocholesterolemic effect of probiotics depends on the species of the bacteria. This hypocholesterolemic effect has been suggested to be caused by more than one mechanism. For example lactic acid bacteria exert hypocholesterolemic effect by assimilating endogenous or exogenous originated cholesterol in intestinal tract or deconjugating bile acids (Gilliland et al., 1990). In addition, it has been reported that cholesterol and free bile acids bound to the cellular surface of microorganism or co-precipitate with free bile acids by probiotics (Guo & Zhang, 2010).

The recent researches have revealed that probiotics affect gene expression of carrier proteins which are responsible for cholesterol absorption. The protein called Niemann-Pick C1-like 1 (NPC1L1) which is abundantly expressed on the surface of enterocytes, plays a key role on the absorption of cholesterol from intestines. Reduction or inhibition of expression levels of this protein leads to a decrease in plasma cholesterol levels. The probiotic *Lactobacillus acidophilus* (American type culture collection) ATCC 4356 reduced NPCIL-1 gene expression and inhibited the cellular uptake of micellar cholesterol in Caco-2 cells. Soluble effector molecules secreted by ATCC 4356 were shown to be responsible for the decrease in NPC1L-1. Furthermore, ATCC 4356 mediated this effect partly through the liver X receptors (LXR) (Huang & Zheng, 2010).

6. Probiotics and enteric nervous system

Enteric nervous system (ENS), which is located in the wall of the digestive tract, is a neural network called as second brain that is consisted of sensory neurons, motor neurons, inter neurons and glial cells. It regulates complicated reflexes, motility and secretory functions of digestive tract. Although it is connected to central nervous system, ENS can regulate the

function of its target organ without input from the central nervous system (CNS) (Gershon, 2005).

There is a mutual communication between CNS and microorganisms in the digestive tract. The central nervous system affects microorganisms by chancing motility, secretion, and permeability of digestive tract or via various mediators that are secreted by neuro-endocrine cells (Barbara et al., 2005). Microorganisms in the digestive tract affect functions of ENS and CNS via direct or indirect mechanisms. Microorganisms both affect development of sensory and motor neurons and induce plasticity.

Microorganisms in intestines communicate with nervous system via epithelial cells, various receptors or cells in lamina propria. Enterochromaffin cells play a key role in this communication. They function such as a transducer and provide a link between intestinal lumen and ENS (Indrio & Neu, 2011).

Effects of microorganisms in intestinal tract on nervous system occur via more than one mechanism. They affect development of sensory and motor neurons in gut by secreted substances or fermented products. For example SCFA, which is a fermented product of microorganisms in digestive tract, may affect motor activity in digestive tract (Soret et al., 2010). Furthermore, certain mediators secreted by immune cells which are activated by microorganisms in intestinal tract are effective on the regulation of ENS. Because, enteric neurons have receptors which are responsive to immune cells secreted mediators. For example, secretion of substances such as histamine, interleukin-6, leukotrienes, 5-hydroxytryptamine, platelet activating factor, mast cell proteases, adenosine, interleukin-1β, prostaglandins as a result of stimulation of mast cells affect functions of ENS by connecting to the receptors on the neurons of ENS (Wood, 2007).

Bacteria including probiotics can be considered as a chemical factory producing biologically active substance such as neurotransmitters and neuromodulators (Wang et al., 2010). It has been determined that *Lactobacillus* and *Bifidobacterium* produce GABA, *Escherichia, Bacillus* and *Saccharomyces* produce norepinephrine, *Candida, Streptococcus, Escherichia* and *Enterococcus* produce serotonin, *Bacillus* produce dopamine, *Lactobacillus* produce acetylcholine (Lyt, 2011).

It has been determined that *Lactobacillus reuteri* increases the excitability of myenteric AH cells in rats by inhibiting calcium dependent potassium channels (Kunze et al., 2009). The same researches have also reported that activity of ENS was inhibited as a result of the effect of *Lactobacillus reuteri* on AH cells (Whang et al., 2010). Because ENS depresses intestines motility, inhibition of ENS causes an increase in motility.

Probiotics reveal their effects by changing neuro-chemical characteristics of enteric neurons. Kamm et al. (2004) have reported that the numbers of neurons containing calbidin, which is a multiple calcium binding protein, decreased in jejunum of pigs supplemented with *Sacharomyces boulardii.* Similarly Giancamillo et al. (2010) have reported that the density of galaninergic and calcitonin gene-related peptide (CGRP) positive neurons increased in submucosal plexus of ileum of *Pediococcus acidilactici* treated pigs. Galanin is effective on peristaltic activity, secretion, blood flow and eating behaviors, and CGRP is effective on the modulation of sensory functions and the regulation of activity of smooth muscle. Furthermore, the same researchers have determined that density of glial cells in ileums' inner and outer sub mucosal plexus was increased in *Pediococcus acidilactici* treated pigs.

Probiotics have been used in the treatments of neuromotoric and sensory functional disorders of digestive tract since their effects on ENS have been revealed. For example, it has been reported that functional disorders such as delayed gastric emptying, increased visceral perception and abnormal feeding pattern which occurs in mice due to *Helikobacter* infection, were treated by supplementation of *Lactobacillus rhamnosus* R0011 and *Lactobacillus helveticus* R0052 (Verdu et al., 2008).

Probiotics in digestive tract affect central nervous system by both ENS and parasympathetic fibers that innervates digestive tract. However this effect is probably species specific. For example, *Lactobacillus reuteri* changes mRNA expressions of $GABA_A$ and $GABA_B$ receptors in central nervous system. The changes in these receptors have found to be related with anxious and depressive-like behaviors (Cryan & O'Mahony, 2011). Similarly it has been reported that *Bifidobacterium longum* has anxiolytic effect and decreases the excitability of ENS (Bercik et al., 2011).

7. The effect of probiotics on the intestinal barrier functions

Intestinal barrier is a morphologic and physiologic structure placed between tissues and intestinal lumen which is known as external environment and it ensures continuing of events such as absorption and secretion between them. Intestinal lumen consists of microclimate on epithelial cells and lamina propria under epithelium. It regulates nutrients absorption, water and ion fluxes, and represents the first defensive barrier against toxins and enteric pathogens. Intestinal barrier consists of internal and external layers; the internal layer includes intestinal epithelial cells and tight junctions (TJ), the external layer includes bacteria and a mucus layer (Catalioto et al., 2011).

The intestinal epithelium is formed by a monolayer epithelial cells, the spaces between epithelial cells is sealed by tight junctions. Tight junctions are specific structures comprised of transmembrane proteins. Microclimate consists of unstirred water layer, glycocalyx, and mucus layer. Lamina propria is a layer existed under epithelial cells. In this layer there are cells of innate and acquired immunity secreting immunoglobulins and cytokines which are substantial for intestinal barrier.

Proper intestinal barrier function is essential for maintaining optimal health and balance throughout the body. The epithelium of the intestinal mucosa prevents the passage of commensal and pathogenic microorganisms. Therefore, it is the first line of defense against luminal antigens and toxins. An impairment of this intestinal barrier is critical for pathogenesis of several diseases such as inflammatory bowel disease, celiac disease (Chichlowski et al., 2008) and atopic dermatitis (Rosenfeldt et al., 2004).

Development of physical and functional intestinal barrier begins during embryonic period. In human, enterocytes appear in intestinal mucosa at 8^{th} weeks, and TJ appear at 10^{th} weeks of pregnancy. Functional immune barrier becomes functional after the formation of panet cells at 12^{th} weeks. In this period, panet cells produce antimicrobial defensins and lysozymes. Mucins, which start to be expressed at 6.5^{th} weeks of pregnancy and increase in time, constitute functional barrier. Although the development of intestinal barrier begins at prenatal period, it continues through postnatal period (Patel & Lin, 2010). Because, intestinal barrier is not yet fully developed in preterm infants, aberrant inflammatory and apoptotic responses to bacteria may occur. When premature infants

treated with probiotics, bacteria used as probiotic easily pass lamina propria and trigger immune reaction there.

It has been determined by *in vivo* and *in vitro* studies that probiotics strengthen intestinal barrier. This effect occurs through species specific various mechanisms. These mechanisms are the inhibition of apoptosis of epithelial cells, the regulation of TJ proteins expression and the distribution, prevention of attachments of pathogens to mucosa, and the regulation of mucus secretion.

7.1 Tight junction protein expression

The intestinal bacteria or probiotics change the expression and distribution of TJ proteins (Mennigen & Bruewe, 2009). Several studies investigated the effects of different probiotics on TJ protein expression and distribution under pathological conditions. Occludin is an integral plasma-membrane protein located at the TJs. Zonula occludens-1 (ZO-1) is a peripheral membrane protein and it is found to be associated with the cytoplasmic surfaces of TJs (Gottardi et al., 1996). Probiotic bacteria *Streptococcus thermophilus* and *Lactobacillus acidophilus* prevent the reduction in phosphorylation of occludin and zonula occludens-1 (ZO-1) caused by enteroinvasive *Escherichia coli* (EIEC) infection (Resta-Lenert & Barrett, 2003). Re-distribution of ZO-1 protein has been observed after epithelial cells were treated by a pathologic bacterium *Salmonella dublin*. However, treatment of epithelial cells with multi-microbe probiotic product VSL#3 prevented the redistribution of ZO-1 (Ng et al., 2009).

7.2 Epithelial adherence and pathogen exclusion

Many intestinal bacteria can adhere to the outer mucus layer to form a biofilm on their surface (Guarner & Malageda, 2003). This is an important mechanism for intestinal barrier. Three different situations in favor of the host and against pathogens should be considered. One of them is exclusion of pathogens by probiotics competitively. The second is the prevention of pathogen adhesion. And the third is displacement of adhered pathogen. Sherman et al. (2005) have reported that *Lactobacillus rhamnosus* and *acidophilus* could adhere to intestinal epithelial cells *in vitro* and pre-treatment of these probiotic strains reduced the binding of EPEC and EHEC. Additionally, *Lactobacillus* strains can directly compete with other pathogens, such as *Salmonella* species, for binding sites on human mucins or Caco-2 cell surfaces. It has been observed that the mentioned probiotics can also displace bound pathogens, although more slowly and to a lesser extent (Lee et al., 2003). There is a competition between pathogens and probiotics for sources of nutrients as well as a competition for adherence to mucosa or displacement from mucosa. This competition is useful for exclusion of pathogens and for strengthening intestinal barrier.

7.3 Mucus secretion

It has been reported by *in vivo* and *in vitro* studies that certain bacteria contribute to strengthen mucosal barrier by increasing mucus secretion. Mattar et al. (2002) reported that *Lactobacillus casei* GG increased mucin expression in the human intestinal cell lines Caco-2 (MUC2) and HT29 (MUC2 and MUC3), thus blocking pathogenic *Escherichia coli* invasion and adherence. Additionally, Otte & Podolsky (2004) observed that VSL#3 increased

expression of MUC2, MUC3 in HT29 cells. Probiotics induce this mucus expression increasing effect by modifying gene expressions. For example, it has been observed that MUC2 and MUC3 mRNA expressions were increased after incubation of epithelial cells with *Lactobacillus plantarum* 299v (Mack et al., 1999). Similarly Caballero-Franco et al. (2007) have reported that basal luminal mucin content increased by 60% in Wistar rats that were orally administered the probiotic mixture VSL#3 on a daily basis for seven days. In addition, they exposed isolated rat colonic loops to the VSL#3 probiotic formula, which significantly stimulated colonic mucin (MUC) secretion and MUC2 gene.

Probiotics also contributes to strengthening of intestinal barrier with some mechanisms other than above mentioned ones. For example, Polyphosphate (poly-P) is produced by probiotics and it is a bioactive molecule that induced cytoprotective heat shock protein through activation of the integrin–p38 mitogen-activated protein kinase pathway, and it prevents oxidant-induced intestinal barrier weakening. Furthermore, poly-P ameliorated epithelial injury (Segawa et al., 2011). It has been reported that multi-microbe probiotic product VSL#3 normalized monolayer permeability and conductance in stimulated tissues, thus strengthened barrier integrity (Madsen et al., 2001). It has been determined that *Lactobacillus rhamnousus* GG prevented cytokine induced apoptosis in young adult mouse colon cell model (YAMC) and human colonic epithelial carcinoma cell line (HT29) (Yan & Polk, 2002).

8. References

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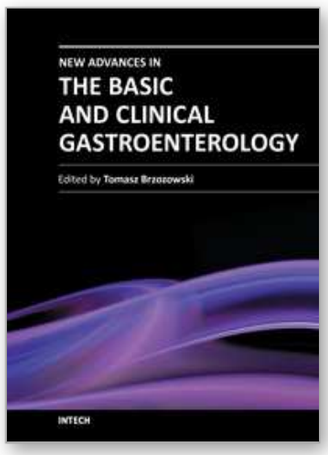

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The purpose of this book was to present the integrative, basic and clinical approaches based on recent developments in the field of gastroenterology. The most important advances in the pathophysiology and treatment of gastrointestinal disorders are discussed including; gastroesophageal reflux disease (GERD), peptic ulcer disease, irritable bowel disease (IBD), NSAIDs-induced gastroenteropathy and pancreatitis. Special focus was addressed to microbial aspects in the gut including recent achievements in the understanding of function of probiotic bacteria, their interaction with gastrointestinal epithelium and usefulness in the treatment of human disorders. We hope that this book will provide relevant new information useful to clinicians and basic scientists as well as to medical students, all looking for new advancements in the field of gastroenterology.

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