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Emerging Approaches for the Treatment of Fat Malabsorption Due to Exocrine Pancreatic Insufficiency

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1. Introduction

The main purpose of the gastrointestinal tract is to digest and absorb nutrients (fat, carbohydrates, and proteins), micronutrients (vitamins and trace minerals), water, and electrolytes. Digestion involves both mechanical and enzymatic breakdown of food. Mechanical processes include chewing, gastric churning, and the to-and-fro mixing in the small intestine. Enzymatic hydrolysis is initiated by intraluminal processes requiring gastric, pancreatic, and biliary secretions. The final products of digestion are absorbed through the intestinal epithelial cells.

Malabsorption is a state arising from abnormality in absorption of food nutrients across the gastrointestinal (GI) tract. Depending on the abnormality, impairment can be of single or multiple nutrients leading to malnutrition and a variety of anaemias. Symptoms of malabsorption are varied because the disorder affects so many systems. General symptoms may include loss of appetite (anorexia), weight loss, fatigue, shortness of breath, dehydration, low blood pressure, and swelling (edema). Nutritional disorders may cause anemia (lack of iron, folate and vitamin B12), bleeding tendency (lack of vitamin K), or bone disease (lack of vitamin D). Gastrointestinal symptoms include flatulence, stomach distention, borborygmi (rumbling in the bowels), discomfort, diarrhea, steatorrhea (excessive fat in stool) and frequent bowel movements (Bai, 1998). Intestinal malabsorption can be due to : mucosal damage (enteropathy), congenital or acquired reduction in absorptive surface, defects of specific hydrolysis, defects of ion transport, impaired enterohepatic circulation or pancreatic insufficiency (Walker-Smith & al.,2002). This chapter will particularly focus on fat malabsorption, the overriding problem caused by severe pancreatic insufficiency.

Pancreatic insufficiency is a condition commonly associated with diseases such as pancreatitis or cystic fibrosis. Patients suffering from these pathologies show a shortage of the digestive enzymes necessary to break down food. Hence, a common feature of these diseases is a severe dietary malabsorption due to the poor hydrolysis of lipid in the lumen of small intestine. Digestive lipases are the key enzymes of fat digestion. The most common example of these enzymes is human pancreatic lipase. Nevertheless, the human lipases include the pre-duodenal lingual and gastric lipase, the extra-duodenal pancreatic, hepatic,

lipoprotein and the recently described endothelial lipase. In this chapter, a short basic overview of these fat-digesting enzymes and their physiological contribution to fat digestion is first presented. Thereafter, pathophysiology of fat malabsorption resulting from exocrine pancreatic insufficiency, clinical symptoms, incidence and diagnosis of the pathology are described as well.

Standard strategies for exocrine pancreatic insufficiency management are based on oral administration of porcine derived pancreatic extracts. Unfortunately, this approach is being unsatisfactory for many reasons. Greater attention has been paid over the last decade to optimize correction of fat malabsorption and essential fatty acid deficiency in order to improve the quality of life and extend the life span of patients with severe pancreatic insufficiency. Hence, we interestingly discuss herein drawbacks of therapeutic use of currently available lipase preparations before focusing mainly on research forces joined for the development of new oral enzyme substitution approaches and future promising opportunities to treat intestinal fat malabsorption caused by exocrine pancreatic insufficiency.

2. Human digestive lipases

Lipases are key enzymes responsible for digesting lipids in the digestive system. In humans, gastrointestinal lipases include pre-duodenal lipases (gastric lipase and lingual lipase) and the other members of the lipase gene family: pancreatic, hepatic, lipoprotein and endothelial lipases. The chromosomal localization of genes encoding these lipases and their tissue of origin has been described (Table 1).

Lipase	Chromosomal localization of gene	Tissue of origin	References
Lingual lipase	-*	Serous glands of the tongue	Hamosh, 1990
Gastric lipase	10q23.2	Fundic mucosa of the stomach	Bodmer & al., 1987
Pancreatic lipase	10q26.1	Pancreas	Sims & al., 1993
Hepatic lipase	15q21–q23	Liver	Ameis & al., 1990
Lipoprotein lipase	8p22	Adipose, heart, skeletal muscle	Wion et al., 1987
Endothelial lipase	18q21.1	Endothelial cells, liver, lung, kidney, placenta	Hirata et al., 1999

* Unknown data

Table 1. Human digestive lipases

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2.1 Lingual lipase

The serous von Ebner glands of the tongue secrete lingual lipase in the saliva. Unlike rodents, lingual lipase is present in trace amounts in humans (Hamosh, 1990). Human lipase purified from lingual serous glands or gastric juice has a MW of 45 kDa to 51 kDa but tends to aggregate (MW 270-300 kDa and 500 kDa) and is highly hydrophobic (Hamosh, 1990). Lingual lipase has unique characteristics including an optimum activity at pH 4,5 – 5,4 and ability to catalyze reactions without bile salts (Hamosh & Scow, 1973). Lingual lipase breaks down short and medium chain saturated fatty acids and helps in their digestion. It has been stated that 10 to 30% of dietary fat is hydrolyzed in the stomach by lingual lipase. The enzyme uses a catalytic triad consisting of Aspartatic Acid-203 (Asp), Histidine-257 (His), and Serine-144 (Ser), to initiate the hydrolysis of a triglyceride into a diacyglyceride and a free fatty acid (Hamosh & Scow, 1973). Secreted in the buccal cavity, lingual lipase is one of the key components that make the digestion of milk fat in newborns possible. In humans lipolytic activity is present in gastric aspirates as early as 26 weeks of gestational age which is evidence enough for the fact that lingual lipase is present at birth (Hamosh, 1979). New born infants indeed secrete only low amounts of pancreatic lipase and bile salts and it has been demonstrated that pancreatic lipase alone does not readily hydrolyze a lipid emulsion as well as native milk fat globules (Miled & al., 2000).

2.2 Gastric lipase

Gastric lipase (EC 3.1.1.3) is the predominant pre-duodenal lipase in humans. The enzyme is secreted in the gastric juice by the chief cells of fundic mucosa in the stomach (Moreau & al., 1988). The pre-duodenal enzyme was purified from human gastric aspirates and its N-terminal amino-acid sequence was determined. The amino-acid sequence from the isolated protein and the DNA sequence obtained from the cloned gene indicated that human gastric lipase consists of a 379 amino acid unglycosylated polypeptide with a molecular weight of 43 162 Da (Bodmer & al., 1987). However, native human gastric lipase (HGL) (molecular weight 50 kDa) is a highly glycosylated protein with four potential glycosylation sites (Bodmer & al., 1987). Human gastric and rat lingual lipase share a high degree of sequence homology and have identical gene organizations (Lohse & al., 1997). Gastric lipase belongs to the α/β-hydrolase-fold family. It possesses a classical catalytic triad (Ser-153, His-353, Asp-324) and an oxyanion hole (backbone NH groups of Gln-154 and Leu-67) analogous to serine proteases (Roussel & al., 1999). It has an optimum pH activity around 5.4, hydrolyzes long-, medium- and short-chain triacylglycerols and do not require bile acid or colipase for optimum enzymatic activity (Denigris et al., 1985). For many years, the exact physiological contribution of gastric lipase to the overall process of lipolysis was unknown. Carrière et al. (1993a) established, for the first time, that most of the HGL secreted in the stomach was still active in the duodenum. They estimated that the gastric lipase contribution in the hydrolysis of triglycerides is about 25 %. The stereoselectivity of HGL toward triglycerides was also investigated. It was clearly demonstrated that HGL shows a stereopreference for the sn-3 position of the triglyceride (Rogalska & al., 1990).

Hence, gastric lipase, together with lingual lipase, make up 30% of lipid hydrolysis occurring during digestion in the human adult, with gastric lipase contributing the most of the two acidic lipases. In neonates, these acidic pre-duodenal lipases are much more important, they have the unique ability to initiate the degradation of maternal milk fat globules.

2.3 Pancreatic lipases

A limitation of acidic lipases is that they remove only one fatty acid from each triacylglycerol. The free fatty acid can readily cross the epithelial membrane lining the gastrointestinal tract, but the diacylglycerol cannot be transported across. Hence, hydrolysis of dietary triacylglycerols by both gastric and pancreatic lipase is essential for their absorption by enterocytes. Human pancreatic lipase (HPL) (EC 3.1.1.3) is produced by the pancreatic acinar cells. The lipase is located into the zymogen granules, together with many other enzymes and secreted into the intestinal lumen together with the bile (Miled & al., 2000). Contrary to most of the pancreatic enzymes which are secreted as proenzymes and further activated by proteolytic cleavage in the small intestines, HPL is directly secreted as an active enzyme. Purified from pancreatic juice, the protein showed to have a molecular weight of 48 kDa (De Caro & al., 1977) and has been characterized as a glycoprotein consisting of 449 amino acid polypeptide (Lowe & al., 1989). The resolution of the HPL 3D structure (Fig.1) revealed the presence of a catalytic triad (Ser^{152}-Asp^{176} –His^{263}) similar to that found in other serine hydrolases, Ser^{152} being part of the G-X-S-X-G consensus sequence (Lowe & al., 1989). Pancreatic lipase acts maximally around pH 8-9 (Winkler et al., 1990) and was found to be poorly stereoselective (Rogalska & al., 1990). Unlike pre-duodenal lipases, pancreatic lipase requires colipase—a pancreatic protein—as cofactor for its enzymatic activity (Fig.1). Colipase relieves phosphatidyl choline-mediated inhibition of the interfacial lipase–substrate complex, helps anchor the lipase to the surface and stabilizes it in the 'open', active conformation (Brockman, 2000; Lowe, 1997).
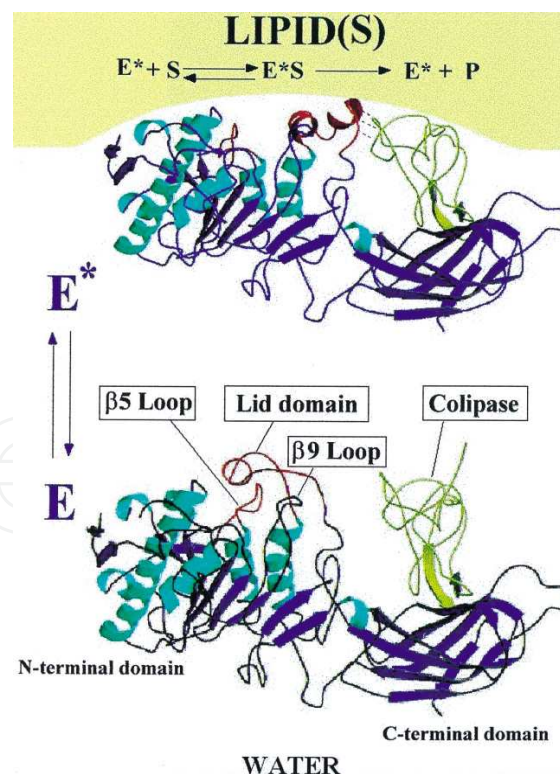

Fig. 1. 3-D Structure of the HPL-procolipase complex in the closed conformation (E) and in the open conformation (E*). These two diagrams show the conformational changes in the lid, the β-5 loop and the colipase during interfacial activation (Adapted from Miled et al., 2000 as cited in van Tilbeurgh et al., 1992; 1993).

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The lipase gene family includes also two other pancreatic proteins: pancreatic lipase related proteins 1 and 2, with strong nucleotide and amino acid sequence homology to pancreatic triglyceride lipase. All three proteins have virtually identical three-dimensional structures (Lowe, 2000). Of the pancreatic triglyceride lipase homologues, only pancreatic lipase related protein 2 has lipase activity (Table 2).

Enzyme Name	Substrate specificity	References
Pancreatic lipase	Triglycerides (lipid-droplet)	Thirstrup & al., 1994
Pancreatic lipase related protein 1 (PLRP1)	Unknown Inhibitory effect of HPL (regulatory effect of TG digestion in the duodenum?)	Crenon & al., 1998 Berton & al., 2009
Pancreatic lipase related protein 2 (PLRP2)	Broad range of substrate specificity Triglycerides (milk lipid-droplet) Synergistic effect of HPL (regulatory effect of TG digestion in the duodenum?) Phospholipids Galactolipids Esters of vitamin A	Berton & al., 2009 Thirstrup & al., 1994 Sias & al., 2004 Reboul & al., 2006
Carboxyl ester lipase	Nonspecific enzyme Esters of lipid-soluble vitamins Esters of cholesterol Triglycerides, diglycerides, monoglycerides Phospholipids Ceramides	Hui & Howles , 2002
Phospholipase A2	Phospholipids	Verheij & al., 1983

Abbreviations: HPL, human pancreatic lipase; TG, triglycerides

Table 2. Human pancreatic enzymes involved in lipid digestion

It should be stressed that adult pancreas also produces an enzyme equivalent to the colipase-dependant pancreatic lipase (CDL) called bile-salt-stimulated lipase (BSSL) or carboxyl ester lipase (EC 3.1.1.1) (Hui & Howles, 2002). Originally discovered in milk of humans and various other primates (Swan & al., 1992), BSSL participates to the intestinal digestion of dietary lipids (Table 2). While colipase-dependent pancreatic lipase facilitates the uptake of fatty acids, bile-salt-stimulated lipase facilitates the uptake of free cholesterol from the intestinal lumen (Sahasrabudhe & al., 1998). A distinguishing feature of this 722 - amino acid native protein is that it requires primary bile salts for the hydrolysis of emulsified long chain triacylglycerols (Sahasrabudhe & al., 1998).

The exocrine pancreas secretes another group of phospholipid-hydrolyzing enzymes including phospholipase A1 (EC 3.1.1.32), and phospholipase A2 (EC 3.1.1.4). These enzymes are secreted in their zymogen form and activated by trypsin on entering the duodenum (Nouri-Sorkhabi & al., 2000).

PLA1 catalyzes the hydrolysis of fatty acids exclusively at the sn-1 position of phospholipids. A free fatty acid (FFA) and a lysophospholipid (lysoPL) are the products of this reaction. However, this class of phospholipase is not well understood, and no crystal structures exist. The assignment of a function for this pancreatic enzyme has yet to be firmly established (Richmond & Smith, 2011).

In intraluminal digestion, phospholipase A2 is primarily responsible for hydrolyzing phosphatidyl-choline to 2-lysophophatidyl-choline. This reaction is important in triglyceride digestion as the amphipathic phosphatidyl-choline, in a manner similar to bile salts, will adsorb to the surface of the lipid droplets, preventing contact between the lipase-colipase complex and its lipid substrate. Hydrolysis of phosphatidyl-choline by phospholipase 2 will allow desorption of lysophosphatidyl-choline, which is water soluble. The subsequent mucosal absorption of lysophosphatidyl-choline is important in the generation of enterocyte phospholipids and lipoproteins and, thus, chylomicron formation (Nouri-Sorkhabi & al., 2000).

2.4 Hepatic lipase

As the name suggests, hepatic lipase (EC 3.1.1.3) is synthesized mostly by hepatocytes in the liver and found localized at the surface of liver sinusoidal capillaries (Perret & al., 2002). The human hepatic lipase presents four glycosylation sites, which are localized at positions 20, 56, 340, and 375, and a molecular mass around 65 kDa (Ben-Zeev & al., 1994 ; Wolle & al., 1993). Together with lipoprotein lipase (LPL), hepatic lipase (HL) could be considered as a lipase of the vascular compartment (Perret & al., 2002). Unlike pancreatic lipase, hepatic lipase does not require a cofactor for its activity; is stable at high salt concentrations and is inactivated by sodium dodecyl sulfate (Mukherjee, 2003). HL exerts both triglyceride lipase and phospholipase A1 activities, and is involved at different steps of lipoprotein metabolism (Santamarina-Fojo & al., 2004). The preferred physiological substrate of hepatic lipase is triglyceride of intermediate density lipoprotein (IDL) particle, which it hydrolyses to form triglyceride-poor and cholesterol-rich low-density lipoprotein (LDL). Hepatic lipase also converts post-prandial triglyceride rich high-density lipoprotein (HDL) particle (i.e.HDL2) to post-absorptive triglyceride poor HDL (i.e. HDL3) (Mukherjee, 2003).

2.5 Lipoprotein lipase

Lipoprotein lipase (EC 3.1.1.34) (LPL) is a non-covalent homodimeric protein produced mainly by the adipose, heart and muscle tissue and to some extent by macrophages (Camp & al., 1990). LPL is secreted from parenchymal cells as a glycosylated homodimer, after which it is translocated through the extracellular matrix and across endothelial cells to the capillary lumen. After secretion, however, the mechanism by which LPL travels across endothelial cells is still unknown (Braun & Severeson 1992; Mead & al., 2002). The glycosylation sites of LPL are Asn-43, Asn-257, and Asn-359 (Mead & al., 2002). Lipoprotein lipase has multiple functional domains including lipid-binding, the dimer formation, heparin binding, cofactor interaction and fatty acid-binding domains (Santamarina-Fojo & Dugi, 1994). Interaction of the enzyme with the lipoprotein substrate takes place in the lipid-binding domain. This results in a conformational change that leads to the movement of a short helical segment or 'lid' to expose the active site containing the Ser-Asp-His catalytic triad, where hydrolysis of triacylglycerol takes place (Emmerich & al., 1992). As a

homodimer, LPL has the dual function of triglyceride hydrolase and ligand/bridging factor for receptor-mediated lipoprotein uptake. Through catalysis, triacylglycerol present in very low-density lipoprotein (VLDL) and chylomicron particles is converted to triglyceride-poor intermediate-density lipoprotein (IDL) and chylomicron remnants, respectively (Mukherjee, 2003). Apolipoprotein CII (ApoCII) present on VLDL particles is the co-factor required for activating the enzyme (Mukherjee, 2003).

2.6 Endothelial lipase

Endothelial lipase (EC 3.1.1.3) which was firstly characterized in 1999 was also added to the lipase gene family (Jaye & al., 1999). Mature endothelial lipase is a 68 kDa glycoprotein with five potential N-linked glycosylation sites (Yasuda & al., 2010). It has 44% primary sequence homology with lipoprotein lipase, 41% with hepatic lipase and 27% with pancreatic lipase (Choi & al., 2002). The enzyme is secreted by endothelial cells from various tissues like lung, liver, kidney and placenta. However, heart and skeletal muscles do not express endothelial lipase (Jaye & al., 1999). Endothelial lipase differs from the other enzymes of the lipase gene family in the sequence of the 'lid' domain. Its 19-residue 'lid' region is 3 residues shorter and less amphipathic than 'lid' region of lipoprotein or hepatic lipase indicating a different enzymatic function (Jaye & al., 1999). Indeed, unlike lipoprotein or hepatic lipases that have triacylglycerol lipase activity, endothelial lipase has primarily a phospholipase A1 activity. It was suggested that endothelial lipase plays a physiologic role in HDL metabolism probably by catalyzing hydrolysis of HDL phospholipids thereby facilitating a direct HDL receptor-mediated uptake (Cohen, 2003). Endothelial lipase may also facilitate the uptake of apolipoprotein B-containing remnant lipoprotein. As the placental tissue abundantly expresses endothelial lipase, it may also have a role in the development of fetus (Choi & al., 2002).

3. Human dietary lipid digestion process and regulation of pancreatic fluid in healthy state

Protein digestion begins in the stomach with the concomitant action of hydrochloric acid and pepsin, continues with pancreatic proteases in the duodenum, and finishes with numerous brush border peptidases located all over the small intestine (Fieker & al., 2011 as cited in Alpers, 1994). Starch digestion begins in the mouth with salivary amylase, continues with pancreatic amylase, and ends with several intestinal brush border oligosaccharidases (Fieker & al., 2011 as cited in Alpers, 1994). In contrast, the majority of lipid digestion and absorption occurs between the pylorus and the ligament of Treitz. Prior to this step, 5% to 40% of the dietary triglyceride acyl chains are released in the stomach by gastric lipase (Armand & al., 1994, 1996, 1999; Carrière & al., 1993b ; Hamosh, 1990) which continues its action in the duodenum together with pancreatic lipase until these enzymes are degraded by pancreatic proteases. Although a pH of 8 to 9 appears to be optimal for pancreatic lipase activity *in vitro*, bile salts allow the enzyme to work efficiently at a pH of 6 to 6.5 *in vivo* (Borgstrom, 1964; Carrière & al., 2005). HPL is responsible for the hydrolysis of 40% to 70% of triglycerides (Fig.2).

The pancreatic lipase-related 2 protein (hPLRP2), with a broader substrate specificity, hydrolyzes milk triglycerides (Berton & al., 2009) phospholipids (Jayne & al., 2002; Lowe, 2002; Thirstrup & al., 1994) galactolipids (Sias & al., 2004) and esters of lipid-soluble vitamins (Reboul & al., 2006). Carboxyl ester lipase (also called bile salt-stimulated lipase,
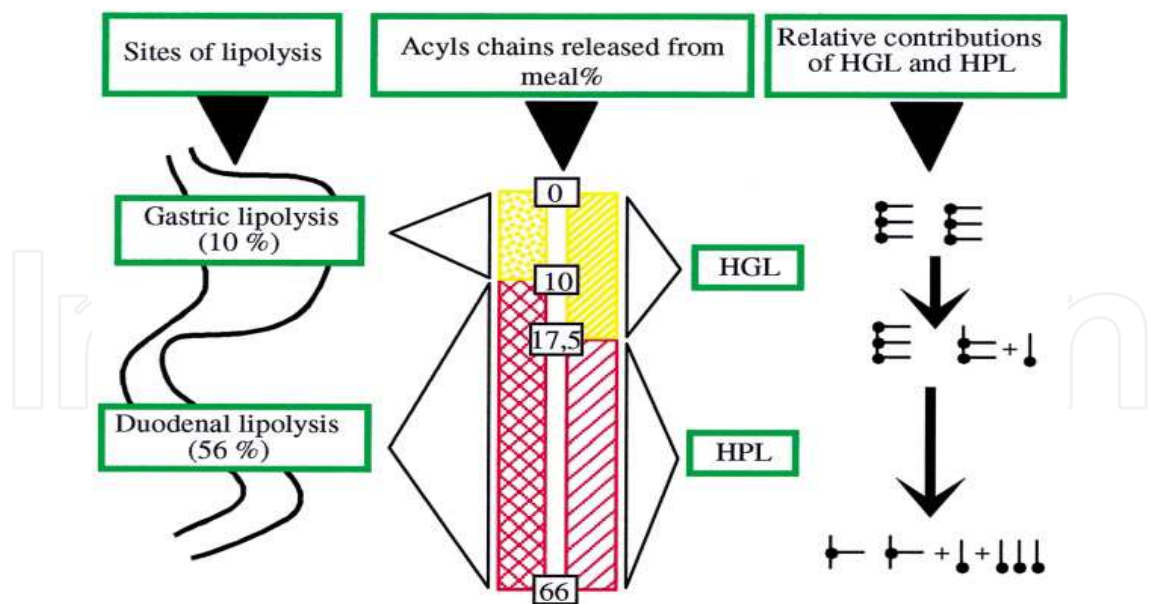
Fig. 2. Schematic representation of the relative contributions of HGL and HPL to the overall digestion of dietary triacylglycerides. On a weight basis, the ratio of pancreatic lipase to gastric lipase total secretory outputs was found to be around four after 3 hours of digestion. The level of gastric hydrolysis was calculated to be 10% of the acyl chains released from the meal triglycerides. Gastric lipase remained active in the duodenum where it might still hydrolyze 7.5% of the triglyceride acyl chains. Hence, globally, during the whole digestion period, gastric lipase hydrolyzes 17.5% of all the triglyceride acyl chains. (Reproduced from Carrière & al., 1993b).

(BSSL)) will hydrolyze triglycerides, diglycerides, phospholipids, and esters of lipid-soluble vitamins and of cholesterol (Hui & Howles, 2002). Phospholipase A2 hydrolyzes phospholipids to lysophospholipids20 which is essential for an optimal absorption of lipid nutrients (Fieker & al., 2011, as cited in Tso, 1994).

Products generated during lipolysis are solubilized in bile salts–mixed micelles and liposomes (vesicles) which allow absorption across the intestinal villi. Once absorbed, the digested lipids are converted back to triglycerides, phospholipids, and esters of cholesterol and of lipid-soluble vitamins, then packaged as chylomicrons and transported through the thoracic duct into the systemic circulation for delivery to various sites throughout the body (Fieker & al., 2011, as cited in Tso, 1994).

To execute this digestive function, postprandial pancreatic juice secretion can increase up to 1 to 2 L per day in response to physiologic stimuli, mainly secretin and vagal output (Lee & Muallem, 2009). Appropriate enzyme delivery in the duodenum is allowed through a specific orchestration of the pancreatic fluid secretion during the fed state. In fact, during the gastric phase, digestion of proteins by pepsin and of triglycerides by gastric lipase generates amino acids and free fatty acids, respectively (Fieker & al., 2011, as cited in Alpers, 1994). When delivered through the pylorus, they become powerful stimulants of the cholecystokinin hormone (CCK) produced by the duodenal endocrine cells which stimulates pancreatic enzymes secretion and controls the gastric emptying rate. The acidic pH of the chyme entering the duodenum stimulates the release of secretin, which increases the secretion of water and bicarbonate ions from the pancreas (Fieker & al., 2011 as cited in

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Solomon, 1994). This gastric phase of digestion represents an important aspect in the overall postprandial regulation of pancreatic secretion. During the intestinal phase, enterohormones, such as CCK, together with neurotransmitters and neuropeptides further stimulate pancreatic secretion (Chey & Chang, 2001). Thus, digestive pancreatic enzyme response to a meal follows a specific pattern in which the degree and duration depend on nutrient composition, caloric content and physical properties of the meal. Enzyme secretion into the duodenum increases quickly reaching peak output within the first 20 to 60 minutes postprandially, then decreasing to a stable level before reaching an interdigestive level at the end of the digestive period, ie, about 4 hours after meal intake (Keller & Layer, 2005).

4. Exocrine pancreatic insufficiency & fat malabsorption

As previously described, the pancreas functions as the main factory for the digestive enzymes. The gland produces pancreatic juice that consists of a mixture of more than two dozen digestive enzymes in the pre-activated form, called zymogens. Zymogens are produced by acinar cells and mixed with a bicarbonate rich fluid that is produced by pancreatic ducts cells (Whitcomb & Lowe, 2007). Trypsin, chymotrypsin, amylase and lipase are responsible for the majority of the enzyme activity derived from the pancreas (Whitcomb & Lowe, 2007). Lipase is one of the most important enzymes because it plays a leading role in the digestion of fat, which is the highest dietary source of calories.

Pancreatic exocrine insufficiency, partial or complete loss of digestive enzyme synthesis, occurs primarily in disorders directly affecting pancreatic tissue integrity (Table 3).

Pancreatic parenchymal disease
Chronic pancreatitis Post-necrotizing acute pancreatitis Cystic fibrosis Pancreatic cancers/tumors Autoimmune pancreatitis
Extrapancreatic disease
Celiac disease Inflammatory bowel disease Diabetes mellitus Zollinger-Ellison syndrome
Postsurgical states
Gastric resection Whipple's pancreaticoduodenectomy Short bowel syndrome Bariatric surgeries (eg, gastric bypass)

Table 3. Conditions Causing EPI (adapted from Keller et al., 2009).

It is most frequently due to chronic pancreatitis (in adults) or cystic fibrosis (in children) (Keller & al., 2009). Other pancreatic causes include acute pancreatitis, pancreatic tumors and pancreatic surgery (Table 3).

While protein and starch digestion are usually maintained at a normal physiological level even in severe cases of pancreatic insufficiency, lipid malabsorption becomes the overriding problem and causes many of the clinical symptoms and nutritional deficiencies.

4.1 Pathophysiology

Clinically evident EPI occurs only when 90% of the function is lost and the secretion of pancreatic enzymes is less than 10% of normal (Lankisch & al., 1986; Layer & al., 1986). In chronic pancreatitis, an earlier decrease of lipase secretion is observed in comparison with amylase and protease. This is due to higher susceptibility of lipase to acidic pH caused by concomitant impairment of bicarbonate secretion, higher susceptibility of lipase to proteolytic destruction during small intestinal transit, additional acidic denaturation of bile acids and marked inhibition of bile acid secretion in malabsorptive states (Keller & Layer, 2005). Hence, in case of EPI, fat malabsorption precedes malabsorption of proteins and carbohydrates and is clinically more apparent. Additionally, due to the low bicarbonate secretion, the intraduodenal pH may drop below 4 late postprandially, bile salts may precipitate which leads to a decrease in post- prandial duodenal lipid solubilisation and contribute to impaired lipolysis (Zentler-Munro & al., 1984). The increased presence of lipids and other nutrients in the distal small bowel causes significant alterations in gut motility leading to accelerated gastric emptying and intestinal transit. This results in a marked decrease in the time available for digestion and absorption of nutrients, which also contributes to the malabsorption (Layer & al. 1997). However, more than 80% of carbohydrates can be digested and absorbed in the absence of pancreatic amylase activity and the colonic flora can further metabolizes malabsorbed carbohydrates (Layer & al., 1986). By contrast, gastric lipase, the only extrapancreatic source of lipolytic activity in humans, does not compensate efficiently for pancreatic lipase deficiency although it may be elevated in patients with chronic pancreatitis compared to healthy individuals (Carrière & al., 1993b). That's why fat malabsorption remains the first problem to be considered when treating EPI.

4.2 Clinical symptoms and complications

Maldigestion of fat results in steatorrhoea. In western countries steatorrhoea is diagnosed when daily stool fat content exceeds 7 g during ingestion of a diet containing 100 g fat per day. This corresponds to a decrease of the enteral absorption rate to less than 93% (Dimagno & al., 1973). Steatorrhoea causes symptoms such as foul-smelling, voluminous, greyish, fatty stools, abdominal cramps, bloating and chronic abdominal pain (Pasquali & al., 1996). It may also cause weight loss due to the loss of the highest dietary source of calories (fat contains 38 kJ/g, carbohydrates and protein contain 17 kJ/g) (Rosenlund & al., 1974). Steatorrhoea and weight loss are the overt clinical symptoms of EPI. They usually only occur if pancreatic enzyme secretion falls below 5–10% of normal levels (Keller & al., 2009).

Due to fat malabsorption fat-soluble vitamins (A, D, E and K), magnesium, calcium and essential fatty and amino–acids are insufficiently resorbed (Dutta & al., 1982; Keller & al., 2009) which results in a variety of associated complications. Deficiencies in these vitamins and

nutrients may lead to tetany, glossitis, cheilosis, and in a more progressive stage, to peripheral neuropathy (Dimagno , 1993). Patients with PEI may exhibit low vitamin D levels and develop osteopathy, i.e. osteopenia, osteoporosis and osteomalacia. There are reports on vitamin A deficiency causing night-blindness, visual impairment and other ocular affections. As a consequence of vitamin E and K deficiencies neurologic symptoms or coagulopathy can occur (Keller & al., 2009). There seems also to be an increased risk for cardiovascular events in PEI, independent of life style factors (Gullo & al., 1996).

4.3 Incidence and diagnosis

The prevalence of EPI is increasing with the higher proportion of patients with cystic fibrosis who survive into adult life and the incidence of chronic pancreatitis, which rises in parallel with alcohol consumption. In fact, the incidence of cystic fibrosis is approximately 1 in 2500 live births. The lack of chloride secretion in the pancreatic duct is responsible for severe exocrine pancreatic insufficiency in approximately 85% of CF newborns (Levy, 2011). In case of chronic pancreatitis, an incidence of 8.2 per 100 000 population per year and a prevalence of 26.4 cases per 100 000 along with a 3.6-fold increase in mortality in patients with alcohol-induced chronic pancreatitis compared with a population without chronic pancreatitis has been signaled (Keller & al., 2009). Hence, to avoid malnutrition related morbidity and mortality, it is pivotal to start treatment as soon as EPI is diagnosed.

Several direct and indirect function tests are available for assessment of pancreatic function. Direct invasive function tests like the secretin-caerulein test are still the gold standard with highest sensitivity and specificity. However, their availability is limited to specialized centers, they are costly, time consuming and uncomfortable for the patient (Keller & al., 2009). Determination of fecal elastase is convenient and widely available but its sensitivity is low in mild to moderate cases. Moreover, due to low specificity, it is of limited value for differential diagnosis in patients with diarrhea (Dominguez-Munoz & al., 1995; Stein & al., 1996). Other non-invasive tests such as 13C-breath tests are becoming more important but are not widely established, yet (Dominguez-Munoz & al., 2007).

5. Standard approaches for the treatment of fat malabsorption due to exocrine pancreatic insufficiency

The main focus in the management of EPI is to prevent weight loss, EPI related symptoms, vitamin deficiencies, and to improve the patient's nutritional status. Whatever the aetiology, oral pancreatic enzyme supplements are widely used as the first-line approach to treat malabsorption secondary to exocrine pancreatic insufficiency (Breithaupt & al., 2007).

5.1 Formulations and galenic properties

Pancreatic enzyme preparations (PEPs) are typically a mixture of porcine-derived pancreatic enzymes. These preparations, also called pancreatin, contain a variable mixture of protease, lipase and amylase depending on the brand. Various preparations are commercially available. The main formulations are immediate-release, enteric-coated microspheres and minimicrospheres, enteric-coated microtablets and enteric-coated microspheres with a bicarbonate buffer (Table 4). A Comprehensive table of these preparations has been summarized in other reviews (Krishnamurty & al., 2009, Ferrone & al., 2007).

Formulation	Number of available products	Product example (manufacturer)
Immediate–release formulations	6	Pancrelipase tablets (various manufacturers) Vikokase powder (Axcan Scandipharm)
Enteric-coated microspheres	24	Lipram capsules (Global Pharmaceuticals) Pangestym (Ethex) Pancrelipase capsules (various manufacturers)
Enteric-coated microtablets	7	Pancrease (McNeil) Ultrase (Axcan Scandipharm)
Enteric-coated minimicrospheres	3	Creon capsules (Solvay Pharmaceuticals)
Enteric-coated microsphere with bicarbonate buffer	3	Pancrecarb (Digestive Care)

Table 4. Commercially available pancreatic enzyme formulations (adapted from Krishnamurty et al., 2009)

The uncoated formulations are susceptible to acidic inactivation in the stomach and are currently used largely in clinical practice to treat the pain of chronic pancreatitis and not malabsorption (Chauhan & Forsmark, 2010). The enteric-coated pancreatic enzyme formulations have been developed to solve problems associated with acid-mediated inactivation of pancreatic lipase, especially in patients with EPI who also show low pH values in the small intestine. First generation of these preparations was the enteric coated tablet with diameter of 11-20 mm. Due to their large size, these formulations did not empty into the duodenum as quickly as smaller food particles and did not show any additional benefits over conventional preparations (Meyer & al., 1988; Meyer & Lake, 1997). Next generation of enteric-coated preparations consist of capsules (over 2 mm in size) coated with acid resistant agents designed to release the enzyme between pH 5.0-5.5. No therapeutic benefit of these preparations was seen. Studies of labeled capsules suggest that even with varying sizes of microspheres, the ingested lipid may enter the duodenum in advance of the pancreatic enzyme (Meyer & Lake, 1997). Hence, newer formulations consisting of capsules containing mini-microspheres, pellets or micro-tablets of less than 2 mm in size were designed to promote an adequate intragastric mixture of exogenous enzymes with chyme. Whether the use of these enteric coated mini-microsphere preparations adds any special advantage over the existing treatment options remains, however, subject to great discussion (Halm & al., 1999; Stern & al, 2000).

The most recent innovation in the formulation of pancreatic enzymes supplements has been the development of enteric-coated "buffered" micro-sphere preparations which have 1.5-2.5 mEq of bicarbonate per capsule. Clinical trials conducted to compare these formulations to standard enteric coated microspheres showed controversy results (Brady & al., 2006; Kalnins & al., 2006).

In Europe, availability of preparations varies by country and they are regulated nationally and not by the European Medicines Agency. In products in which the enzyme content has

been standardized, marked variability in particle size, enzyme release, and for some, acid stability has been noted and may result in differences in clinical effect (Walters & Littlewood, 1996; Aloulou & al., 2008; Löhr & al., 2009). In the United States, marked variation in the enzyme content of the various formulations especially with generic products has been attributed to a lack of stringent regulation (Fieker & al., 2011).

5.2 Dosage recommendation and schedule of administration

Some general guidelines are given in spite of the absence of an easy applicable and objective method to establish the adequate dose of oral pancreatic enzymes to treat exocrine pancreatic insufficiency.

In general, the recommended dosage of Pancreatic enzyme supplements (PES) for a main meal (breakfast, lunch, or dinner) ranges from 25,000 to 75,000 units of lipase and from 10,000 to 25,000 units of lipase for snacks, depending on the fat content of the meal (Sikkens et al., 2010). Initial dose must ensure supplementation of 60 UI/min of lipase activity in postparandial chyme throughout the digestive period; hence, dosing is adjusted considering this recommendation and the amount of lipase in the supplement (Krishnamurty et al., 2009) but it is not recommended to exceed 10,000 units of lipase per kg of body weight per meal (Fieker et al., 2011).

The timing of ingestion of the capsules is important to optimize therapeutic efficacy. A recent study compared three different administration schedules using enzyme replacement before, during or after meals. Better lipid digestion was found when giving enzymes during or after meals (Dominguez-Munoz & al., 2005).

5.3 Efficacy assessment of the treatment with pancreatic enzyme supplements

Numerous randomized placebo controlled trials have shown that treatment with pancreatic enzyme supplements improves steatorrhea, as measured by increased fat absorption, reduced fecal fat excretion, decreased stool weight and frequency, improved stool consistency and improved symptom scores (Guarner et al., 1993; O'keefe et al., 2001; Dominguez-Munoz et al., 2005; Safdi et al., 2006, Trapnell et al., 2009; Wooldridge et al., 2009; Whitcomb et al., 2010). Enzyme supplements have been found to improve lipid malabsorption in children even those who are younger than 7 years old (Graff et al., 2010a, 2010b). In yet other studies, increased cholesterol absorption and improved enterohepatic cycling of bile salts have been reported (Dutta et al., 1986; Vuoristo et al., 1992). Moreover, it has been demonstrated that improvement of lipid digestion contributes to effective correction of motility disorders (Mizushima et al., 2004). Altered levels of gastro-intestinal hormones were normalized (Nustede et al., 1991); accelerated gastric emptying and abnormal antroduodenal motility were corrected (Layer et al., 1997).

Even though, randomized controlled trials have suggested, years ago, that non-enteric coated pancreatic enzyme supplements reduce pain in chronic pancreatitis (Isaksson et al., 1983; Slaff et al., 1984), a more recent study did not support the use of these preparations for the relief of pain in all patients (Brown et al., 1997). Unfortunately, pancreatic enzyme supplements were reported to be not sufficient for correcting fat soluble vitamin deficiencies or B12 deficiency without simultaneous vitamin supplementation (Dutta et al., 1982; Bang et al., 1991).

The most surprising fact regarding efficacy assessment of this therapy is that few investigations are made considering nutritional status and quality of life improvements as well as weight gain (Czako et al., 2003; Trolli et al., 2001; Dominguez-Munoz, 2007). Reduction in stool fat achieved by pancreatic enzyme replacement therapy has not been proven by robust research to be correlated with a complete correction of nutritional deficiency in patients with pancreatic insufficiency. Accordingly, an overall assessment of this therapy efficacy is yet dependent on future demonstration of long-term interesting outcomes.

5.4 Safety concerns, side effect and treatment failure

Enzyme replacement therapy using pancrelipase (pancreatin) delayed-release capsules (i.e. Creon®, Solvay Pharmaceuticals, Inc., Marietta, GA, USA) have been available in the United States of America for more than 20 years with very few observed side effects (Krishnamurty et al., 2009). Meanwhile, allergic reactions to the porcine proteins and some others side effects may occur: Pancreatin extracts are prone to form insoluble complexes with folic acid resulting in folate deficiency (Russell & al., 1980). One serious adverse effect has been reported by Smyth et al. (1994, 1995). The authors described five children with cystic fibrosis in which a colonic obstruction developed due to fibrosing colonopathy (FC) after using very high doses of the enteric-coated micro- minisphere preparations (i.e. more than 20000 lipase units/capsule). Fortunately, the cases of reported FC have decreased considerably since the Medicine Control Agency (MCA) recommended in 1994 that the dose of pancreatic enzymes should not exceed 10,000 IU lipase/kg/day in patients with CF (Taylor , 2002 as cited in Medicine Control Agency, 1994).

Recently, Axcan Pharma Inc. and its subsidiaries received safety update reports describing a total of 46 adverse events observed in a clinical study carried out between 01 November 2008 and 31 May 2009 and involving three pancreatic enzyme preparations: ULTRASE®, VIOKASE® and PANZYTRAT® (Table 5). Fifty-three patients were enrolled, 40 of these patients completed the study.

In most cases, adverse effects were single occurrences. Drug ineffectiveness was the most frequently reported adverse effect for ULTRASE® (Table 5). A lack of therapeutic effect was also reported for some other preparations (Kraisinger et al., 1994). In fact, among marketed PEPs, great variability in the amount of enzymes included in each capsule has been noted (Case & al., 2005; US Food and Drug Administration, 2006; Wooldridge & al., 2009) due in part to the manufacturer practice of overfilling capsules to account for enzyme degradation that occurs over the course of the product's shelf life (US Food and Drug Administration, 2004). While instability of the enzymes results in delivery medications that contain less than the packaged amount of enzyme, the practice of "overfilling" in an effort to address enzyme degradation may result in excess enzyme content, resulting in formulations that deliver inadequate or excess amounts of enzyme.

The possible safety risk posed by high-dose enzyme therapy, particularly fibrosing colonopathy , in combination with the issue of enzyme overfill, recently prompted the FDA to require the manufacturers of PEPs to demonstrate drug efficacy and safety in randomized, placebo-controlled trials before approval (Trapnell & al., 2009). The FDA ruled that manufacturers of pancreatic enzyme supplements must file new drug applications

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Cardiac disorders				
Cardio-respiratory arrest	0	1	0	1
Gastrointestinal disorders				
Abdominal pain	0	2	0	2
Abdominal pain upper	1	1	1	3
Abnormal faeces	0	1	0	1
Diarrhoea	1	3	1	5
Dyspepsia	0	1	0	1
Faecal volume increased	1	0	0	1
Frequent bowel movements	1	0	0	1
Gastritis	0	1	0	1
Glossodynia	0	1	0	1
Groin pain	0	1	0	1
Lip swelling	0	1	0	1
Nausea	0	1	1	2
Oral discomfort	0	1	0	1
Steatorrhoea	1	0	0	1
Swollen tongue	0	1	0	1
Tongue ulceration	0	1	0	1
Vomiting	0	0	1	1
General disorders and administration site conditions				
Asthenia	0	1	0	1
Drug effect decreased	1	0	0	1
Drug ineffective	4	0	0	4
Feeling abnormal	0	1	0	1
Product commingling	0	1	0	1
Therapeutic response decreased	0	1	0	1
Injury, poisoning and procedural complications				
Incorrect dose administered	0	1	0	1
Investigations				
Blood glucose increased	1	0	0	1
Blood sodium decreased	0	1	0	1
Blood sugar level fluctuation	0	1	0	1
Drug screen positive	0	1	0	1
Weight decreased	1	0	0	1
Metabolism and nutrition disorders				
Diabetes mellitus	1	0	0	1
Nervous system disorders				
Loss of consciousness	0	1	0	1
Respiratory, thoracic and mediastinal disorders				
Throat irritation	0	1	0	1
Skin and subcutaneous tissue disorders				
Rash macular	0	1	0	1
Urticaria	0	1	0	1

Coded with MedDRA dictionary

Table 5. Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from November 1, 2008, to May 31, 2009 (Reproduced from Page 8 of the Safety Update for NDA 22-222 dated August 4, 2009).

(NDA) to ensure consistent efficacy, safety, and quality of these agents (US Food and Drug Administration, 2006). Therefore, in order to comply with the FDA 2004 mandate, several studies have been recently conducted to ensure safety and effectiveness of some new reformulated pancreatic enzyme supplements such as Creon® 24,000 and EUR-1008 (Zenpep™) (Wooldridge & al., 2009; Trapnell & al., 2009). Nevertheless, these products of animal origin present yet a risk of viral transmission. Accordingly, there remains a need for new alternatives to treat correctly exocrine pancreatic insufficiency.

6. Enzyme replacement therapy: What's in the pipeline?

6.1 Bovine enzymes

Even though bovine enzymes have been suggested as a potential alternative for individuals who refuse to consume porcine products for religious or other cultural reasons; there remain some safety concerns about transmittable pathogens such as Foot and mouth disease and Bovine spongiform encephalopathy from these preparations. Additionally, lipase activity is approximately 75% lower than the porcine preparations (Layer and Keller, 2003)

6.2 Recombinant mammalian/human lipases

Owing to rapid development of plant biotechnology in recent times, Merispase a recombinant mammalian gastric lipase was produced in transgenic corn by Meristem Therapeutics and proposed as new oral substitute for the treatment of pancreatic insufficiency. Dog gastric lipase was selected because it is naturally resistant to inactivation by stomach acids and maintains a high enzymatic activity after passage through the stomach. Enzyme expression was stable over 11 generations with an approximate level of 1,000 mg kg^{-1} kernel (Shama & Peterson, 2008). According to Fieker et al. (2011), this approach could be problematic for several reasons: gastric lipase specific activity is about 10 times lower than that of pancreatic lipase (measured on tributyrin), it is highly sensitive to trypsin proteolysis, and endogenous secretion of gastric lipase can be increased in patients with pancreatic insufficiency because of possible nutritional adaptation. Meanwhile, clinical trials showed that the recombinant gastric lipase is well tolerated and efficient when administered either alone or combined with porcine pancreatic extract to patients with cystic fibrosis (Fieker & al., 2011, as cited by Lenoir et al., 2006, 2008). The highest efficiency is obtained when 250 mg of recombinant gastric lipase is associated with low dose of pancreatic extract (Fieker & al., 2011, as cited by Lenoir et al., 2008). Despite these encouraging results, Mersitem therapeutics went out of business in September 2008 while the product was blocked in clinical phase II trial.

Expected to offer superior safety by decreasing the risk of allergic reactions, recombinant human bile salt- stimulated lipase was suggested as promising candidate for the treatment of lipid malabsorption in pancreatic insufficiency. Human bile salt-stimulated lipase is naturally acid resistant and able to: (i) hydrolyze triglycerides and phospholipids (Lindquist & Hernell, 2010) (ii) generate lysophospholipids necessary for an efficient lipid absorption rate by the small intestine (Fieker & al., as cited by Tso, 1994) (iii) participate in chylomicron assembly and secretion through its ceramidase activity (Hui and Howles, 2002). For these reasons, Swedish Orphan Biovitrum - a leading company focused on treatment of rare diseases developed two preparations of recombinant bile salt-stimulated lipase: Kiobrina for preterm infants and

Exinalda for cystic fibrosis patients. A phase I clinical trial showed that addition of recombinant bile salt-stimulated lipase to standard pancrelipase (Creon) enabled a dose reduction of pancrelipase. The treatment had the advantage of restoring a normal level and pattern of plasma chylomicron secretion (Fieker & al., 2011, as cited by Strandvik et al., 2004). The combined results from two Phase II studies evaluating Kiobrina in preterm infants demonstrated an increase in growth velocity and uptake of long chain polyunsaturated fatty acids such as docosahexanoic acid and arachidonic acid. The safety and tolerability profile of rhBSSL added to formula was similar compared to placebo (Maggio et al., 2010). Based on these encouraging results, Swedish Orphan Biovitrum enrolls in August 2011 the first patient in Kiorbina phase III clinical trial. An open-label exploratory phase II study on Exinalda (rhBSSL) in patients with cystic fibrosis and pancreatic insufficiency has been completed. The aim was to study the effect of Exinalda on fat absorption as well as safety in this patient population. The results showed that Exinalda is safe and tolerable at a dose level of 170 mg three times a day. In terms of efficacy (coefficient of fat absorption CFA) the primary endpoint was not met. Swedish Orphan Biovitrum is now assessing options to continue the development (Swedish Orphan Biovitrum website www. sobi.com).

6.3 Microbial and plant derived lipases

With the aim of developing porcine-free enzyme supplements and in order to avoid the short-life of lipolytic enzymes of pancreatic origin, microbial lipases of fungal or bacterial origin were suggested for replacement therapy. Therefore, potential efficacy of many fungal Lipases derived from *Aspergillus niger* (Griffin & al., 1989), *Rhizopus arrhizus* (Iliano & Lodewijk, 1990), *Rhizopus delemar* (Galle & al., 2004), *Candida cylindracea* (Schuler & Schuler, 2008) and *Yarrowia lipolytica* (Turki & al., 2010a) was investigated. The *Yarrowia lipolytica* lipase seemed to be of potential interest because of its acid and protease-stable properties and its resistance to the detergent action of bile salts as shown *in vitro* (Turki & al., 2010a). Supporting its use as a pharmaceutical, safety assessment of the enzyme in rats showed that there were no toxicologically severe changes in clinical signs, growth, hematology, clinical chemistry, organ weight and pathology related to oral administration of *Yarrowia lipolytica* lipase in animals (Turki & al., 2010b). Actually, a substitute for EPI treatment based on Lip2p is under investigation by Laboratoire Mayoly Spindler, a French pharmaceutical company specialized in gastroenterology therapeutics (Fickers & al., 2011, as cited in http://www.mayoly-spindler.com/). The process development in cGMP conditions for the production of the *Yarrowia lipolytica* MS1819 lipase was completed in 2009 with the Swiss biotech company DSM Nutritional Product Ltd (Fickers & al., 2011, as cited in http://www.dsm.com, press release, December 22th, 2009). In 2010, a drug development partnership was established with Protea Biosciences to initiate phase I/IIA clinical trials in France with the aim of demonstrating safety and proof-of-concept of the therapeutic use of this recombinant lipase (Fickers & al., 2011).

A pipeline preparation Liprotamase (formerly known as ALTU 135 and Trizytek) containing bacterial lipase, fungal protease and amylase was developed by Eli Lilly company (Eli Lilly, IN, USA, www. Lilly.com). An open-label Phase III safety study was carried out in order to evaluate 214 patients, of which 145 CF patients, ages 7 and above, completed 12 months of treatment with Liprotamase. Investigators found that 96 percent of all CF patients who received liprotamase for 12 months maintained or gained weight. Based on key nutritional parameters, the study showed that patients who completed 12 months of treatment with

liprotamase demonstrated that they maintained their nutritional status; and survival in people living with cystic fibrosis was maintained too (Borowitz & al., 2011). Subsequent to the completion of the stage III clinical study on liprotamase, the drug's manufacturer submitted a New Drug Application to the U.S. Food and Drug Administration (FDA) for approval. However, on January 13th of this year, the FDA panel stated that he was not convinced that Liprotamase was any better than the current pancreatic enzyme products available now. The manufacturer disclosed that another clinical trial must be conducted before the FDA will consider the approval of this drug (Eli Lilly, IN, USA, www. Lilly.com).

In yet other approaches, plant acid-stable lipases were suggested as good alternatives to porcine preparations. Hence, considerable attention has focused in these enzymes and suitable techniques for isolating and purifying them have been well documented. A lipase sourced from *Carica papaya* latex has been recently proposed as suitable candidate for use as a therapeutic tool in patients with pancreatic exocrine insufficiency (Abdelkafi et al., 2009). The enzyme showed several biochemical properties enabling it to act in the gastro-intestinal tract like mammalian digestive lipases (Abdelkafi et al., 2009): (i) its activity on long-chain Triacylglycerols reaches an optimum at pH 6.0 in the presence of bile, (ii) it is only weakly inhibited by bile salts, (iii) it shows a similar pattern of regioselectivity to that of human pancreatic lipase, generating 2-Mono acylglycerol and free fatty acids (FFA), the lipolysis products absorbed at the intestinal level, and (iv) it shows significant levels of stability and activity at low pH values at a temperature of 37 °C. Therefore, *Carica papaya* lipase seems to be tailored to act optimally under the physiological conditions pertaining in the gastro-intestinal tract. However, its sensitivity to digestive proteases still needs to be tested.

6.4 Future therapies and new research areas

Development of non-porcine enzyme replacement therapies is currently extended to new research areas including design, by direct molecular evolution, of human pancreatic lipase variants that display lipolytic activity at acidic pH higher than that of the native enzyme. Colin et al. (2008) investigated, first, the feasibility of altering the pH optimum of pancreatic lipase to improve its performances in the intestinal conditions of cystic fibrosis by site-directed mutagenesis. Later, they demonstrated that directed molecular evolution approach combined to a sensitive screening strategy could be useful to improve pancreatic lipase activity at acidic pH. The authors showed that a single round of random mutagenesis was successful in identifying lipase variant with approximately 1.5-fold increased activity at low pH (Colin et al., 2010).

Future therapies may also include structuring food emulsions and creation of functional dietary lipids that are more effectively digested. This new area of research could substantially help patient suffering from pancreatic insufficiency with the design of specific more digestible or absorbable lipid sources. Hence, the addition of specific phospholipids able to enhance lipase activity in enzyme supplements or in formula would both increase lipase activity and, in parallel, enhance lipid nutrient absorption (Fieker et al., 2011).

7. Conclusion

Pancreatic exocrine insufficiency is a condition commonly associated with diseases such as pancreatitis or cystic fibrosis. When pancreatic insufficiency is severe, impaired absorption

of nutrients by the intestines may result, leading to deficiencies of essential nutrients and the occurrence of loose stools containing unabsorbed fat (steatorrhea). A shortage of the digestive enzymes necessary to break down food is the main cause of this dietary malabsorption. Unlike protein and starch digestion, lipid malabsorption is the overriding problem and the main cause of clinical symptoms and nutritional deficiencies. Until recently, approaches used to address problem of fat malabsorption due to pancreatic insufficiency have been focusing primarily on oral administration of exogenous pancreatic enzymes extracted from porcine source. Standard clinical practices dictate administration of lipase 25,000-75,000 units/meal by using pH-sensitive pancrelipase microspheres, along with dosage increases, compliance checks, and differential diagnosis in cases of treatment failure. Various pancreatin preparations are available, however, differences in galenic properties and release kinetics and other factors such as early acid inactivation, under dosage and patient incompliance may decrease clinical efficacy of the treatment. The FDA decreed that all manufacturers of pancreatic enzyme supplements must file new drug applications (NDA) to ensure consistent efficacy, safety, and quality of these agents. Accordingly, improved approaches to treat efficiently problem of fat malabsorption secondary to pancreatic insufficiency are investigated. New alternatives of enzyme substitution therapy are being developed. Emerging therapeutic landscape includes use of porcine free - lipase preparations. Enzyme supplements either from human, mammalian, microbial or plant origins are wisely suggested. Interestingly, newest approaches state the design of acid -stable variants of human pancreatic lipase as well as creation of functional dietary food with specific more digestible/absorbable lipid sources. However, how these pipeline therapies may help meet the ongoing challenges in treating lipid malabsorption in patients with pancreatic insufficiency and improve the long-term outcomes of these patients remains yet to be assessed.

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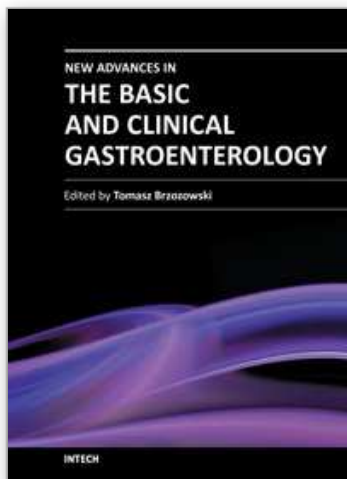
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Edited by Prof. Tomasz Brzozowski

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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