

The exocrine pancreas

Pancreatic enzymes; the missing link in health and disease?

Leo Pruimboom
2014

Abstract

This seminar text reviews various forms of enzyme supplementation used clinically in digestive and absorption disorders. Enzyme supplementation plays an integral role in the management of various digestive disorders, particularly with regard to exocrine pancreatic insufficiency. However, application of enzymes may also be beneficial for other conditions associated with poor digestion including lactose intolerance and coeliac disease. Historically, porcine and bovine pancreatic enzymes have been the preferred form of supplementation for exocrine pancreatic insufficiency. Use of microbe-derived lipase has shown promise with studies indicating benefit similar to pancreatic enzymes, but at a lower dosage concentration and with a broader pH range. Safety and efficacy of enzymes derived from microbial species in the treatment of conditions such as malabsorption and lactose intolerance is promising. Plant-based enzymes, such as bromelain from pineapple, serve as effective digestive aids in the breakdown of proteins. Synergistic effects have been observed using a combination of animal-based enzymes and microbe-derived enzymes or bromelain.

Pancreatic enzyme activity depends on different pathways including local duodenal mechanism and central parasympathetic (acetylcholinergic) signalling. Local and central mechanisms use cholecystokinin as signal. Cholecystokinin is considered an anorexigenic compound and is produced by duodenal gut lining cells. Once pancreatic enzymes are activated, they degrade fats, proteins and carbohydrates in absorbable microsubstances. Insufficiency of the exocrine pancreas could therefore produce malabsorption syndrome, nutritional deficiency (vitamin A, vitamin D and vitamin E), steatorrhea and multiple organ disorder. The use of pancreatic enzyme supplementation has been proven to be effective in several disorders including colitis ulcerosa, morbus Crohn, systemic diseases, irritable bowel syndrome (IBS), chronic and acute pancreatitis and pancreas cancer.

Introduction

Pancreatic exocrine insufficiency is a major consequence of diseases leading to a loss of pancreatic parenchyma (eg, chronic pancreatitis, cystic fibrosis), obstruction of the main pancreatic duct (eg, gallstones, pancreatic and ampullary tumors), decreased pancreatic stimulation (eg, nutritional fibers of cereals and legumes, celiac disease), or acid-mediated inactivation of pancreatic enzymes (microbiota disorders, use of certain medicines, acid based nutrients such as cheese). In addition, gastrointestinal and pancreatic surgical resection (eg, gastrectomy or duodenopancreatectomy) leading to post-cibal asynchrony, decreased pancreatic stimulation (cereal lectin, soy lectin), and loss of pancreatic parenchyma is a frequent cause of pancreatic exocrine insufficiency. The main clinical consequence of pancreatic exocrine

insufficiency is fat maldigestion and steatorrhea (Dominguez-Muñoz 2007). Lipase is the most unstable pancreatic enzyme during gastrointestinal transit most probably due to the high sensitivity of pancreatic lipase to proteolysis and acidic pH. Due to proteolytic degradation, most amylase activity and more than 20% of trypsin activity but only 1% of lipase activity produced by the pancreas and secreted into the duodenum after a pure carbohydrate meal, are still present within terminal ileum. Lipase also suffers irreversible inactivation at acidic pH, which is frequently present within the duodenum and jejunum in patients with pancreatic exocrine insufficiency due to low pancreatic bicarbonatesecretion [zinc deficiency syndrome]. In patients with pancreatic exocrine insufficiency, the reduced luminal action of pancreatic amylase and proteases is compensated for by salivary amylase, intestinal glycosidase, colonic flora, gastric pepsin, and intestinal peptidases. However, it has been generally accepted that digestive action of pancreatic lipase is hardly compensated by extrapancreatic mechanisms. Steatorrhea does not develop until pancreatic lipase output is below 10% of normal, which has been classically interpreted as the consequence of a very large reserve capacity of the exocrine pancreas for enzyme secretion. In contrast, more recent studies have demonstrated a rather linear correlation between inhibition of duodenal lipolysis and fat excretion levels.

This finding is also supported by the fact that human pancreatic lipase-specific activity on meal triglycerides is three orders of magnitude lower than the very high specific activity usually measured under experimental conditions in aspirated duodenal juice. Finally, human gastric lipase output is increased three- to fourfold in patients with pancreatic exocrine insufficiency, which can be responsible for a relevant proportion of dietary triglyceride digestion in these patients. Gastric lipase activity therefore is capable of compensating for pancreatic lipase deficiency in patients with pancreatic exocrine insufficiency, thus explaining at least in part the absence of steatorrhea in patients with more than 10% of normal pancreatic lipase secretion. Despite the proposition by some authors that impairment of lipase secretion occurs earlier than for other enzymes in the context of chronic pancreatitis, which could be an additional factor for fat maldigestion as the major clinical consequence of pancreatic exocrine insufficiency, other authors could not confirm these data; thus, this factor is probably of minor clinical relevance.

Together with abdominal cramps and the typical characteristics of fatty stools associated with steatorrhea (loose, greasy, foul-smelling voluminous stools that are difficult to flush), which are not always evident because patients tend to limit fat ingestion, fat maldigestion causes important clinical problems.

Fat maldigestion can cause deficiency of vitamin D, vitamin A and vitamin E (Dominguez-Muñoz 2007^a). Maldigestion of protein and carbohydrates is able to induce the production of methylmercaptane, putrescine and cadaverine which are responsible for the bad odor of stool, breath and sometimes vagina in people suffering from exocrine pancreas insufficiency (Lewis 1998). The physiological role of these substances is to attack s-adenosylmethionine (SAME) converting it in spermidine (Kakhi 2007). SAME is the universal donor of methyl-groups used by methyltransferases in methylation processes. An excess of the protein based putrifactors could produce a lack of SAME and therefore deficient methylation of certain monoamines such as serotonin with decreased

production of essential melatonin in the gut. Melatonin has been proven to regulate the production of insulin and pancreatic enzymes, as does its precursor triptophan (Jaworek 2007). Triptophan and melatonin are able to increase the production of pancreas enzymes in exocrine pancreas deficiency syndrome and protect the pancreas against chronic stimulation (figures 1 and 2). The use of exogenous triptophan in patients suffering from exocrine pancreas insufficiency syndrome has been proven effective in vitro and in vivo (Jawrok 2007, Leja-Szpac 2004), while human trials still lacking.

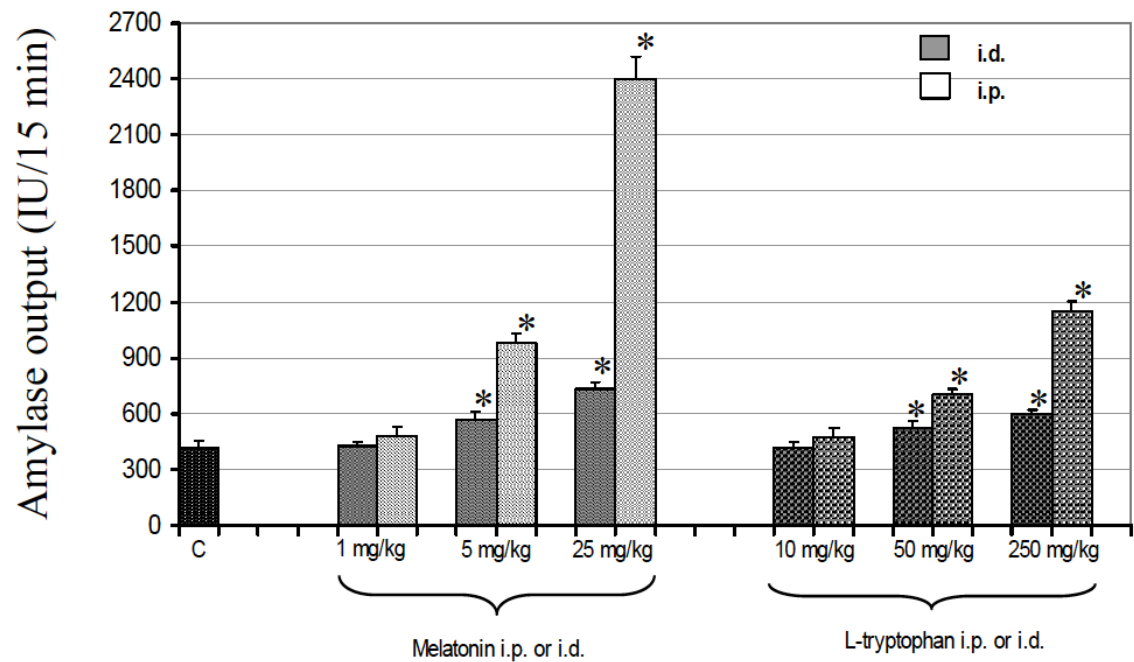


Figure 1 Melatonin and triptophan upregulate the production of pancreas enzymes in exocrine pancreas insufficiency syndrome (Jaworek 2007)

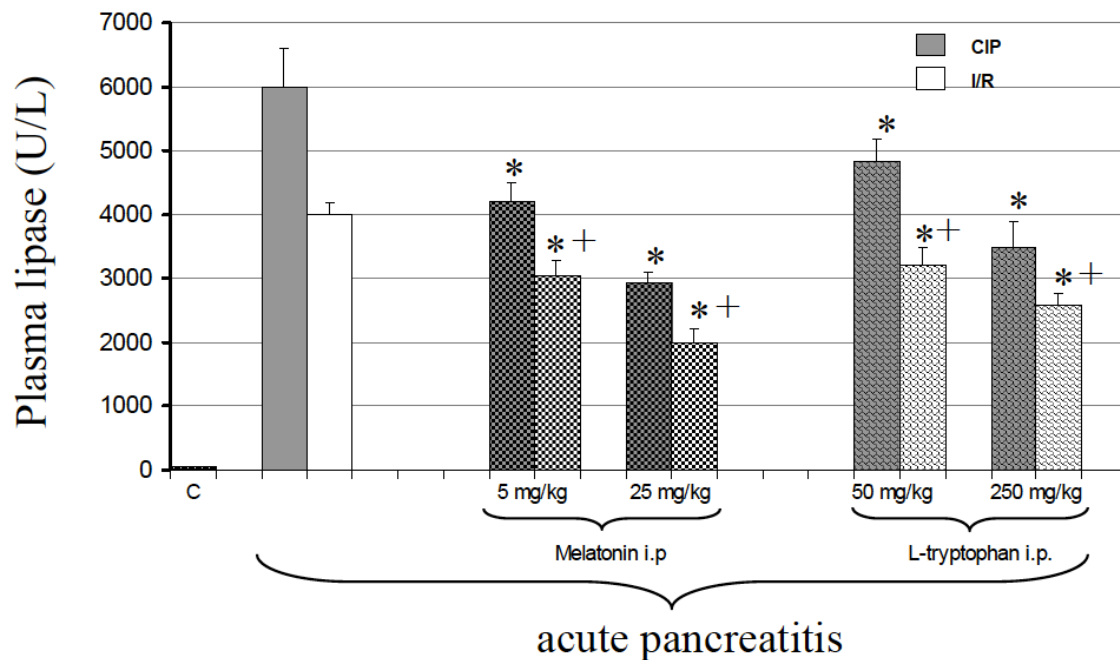


Figure 2 Melatonin and triptophane protect the pancreas against chronic stimulation by caerulein (CIP, a CCK analog) and ischemic insult (Jaworek 2007)

SAMe is further an important precursor of the pancreas protecting compound glutathione. Glutathione functions in the pancreas are 1. protection against oxidative stress and 2. induction of exocytosis of pancreatic enzymes in the duodenal lumen (Braganza 2010). Free radicals play an essential role in the development of exocrine pancreas insufficiency and pancreatitis, mainly by upregulation of the enzyme complex NADPH oxidase (Masumane 2008). NADPH oxidase activity converts oxygen in the superoxide radical which possibly damages the cell membrane of the pancreas cells and the lysosomes in which inactive pancreas enzymes are embedded; Acute pancreatitis could therefore develop.

Pancreatic anatomy

Figure 3 shows the anatomy of a normal human pancreas. The acinar cells produce pancreatic enzymes, whereas the islet cells are responsible for the production of insulin (beta cells of Langerhans), glucagon (alpha cells of Langerhans) and somatostatin (delta cells of Langerhans). Duct cells produce a large amount of bicarbonate through carbon anhydrase activity. The enzymes and the bicarbonate are excreted in the pancreatic ducts, which join the bile duct, reaching the duodenal lumen through the sphincter of Oddi (figure 4).

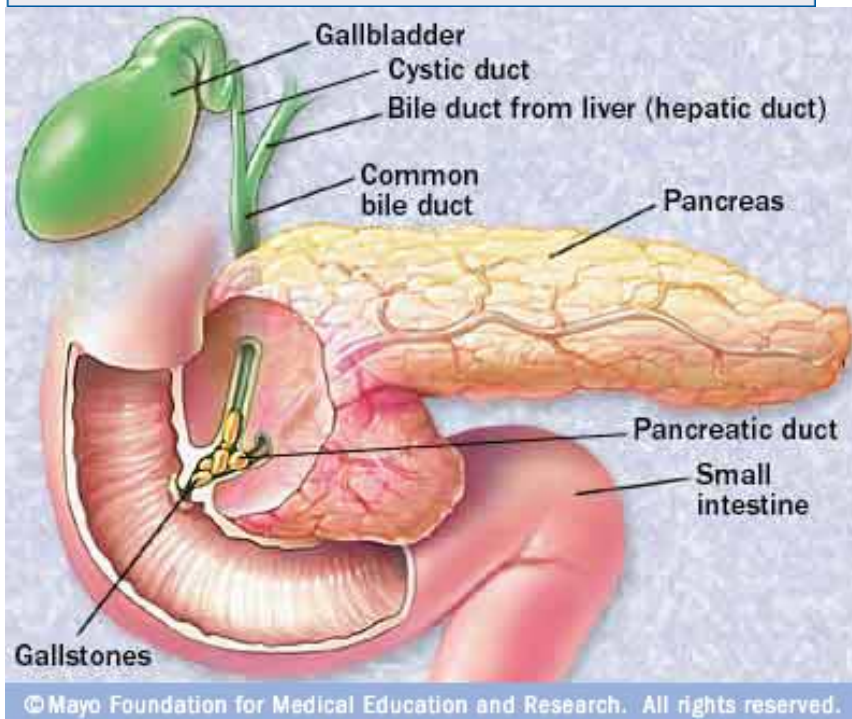
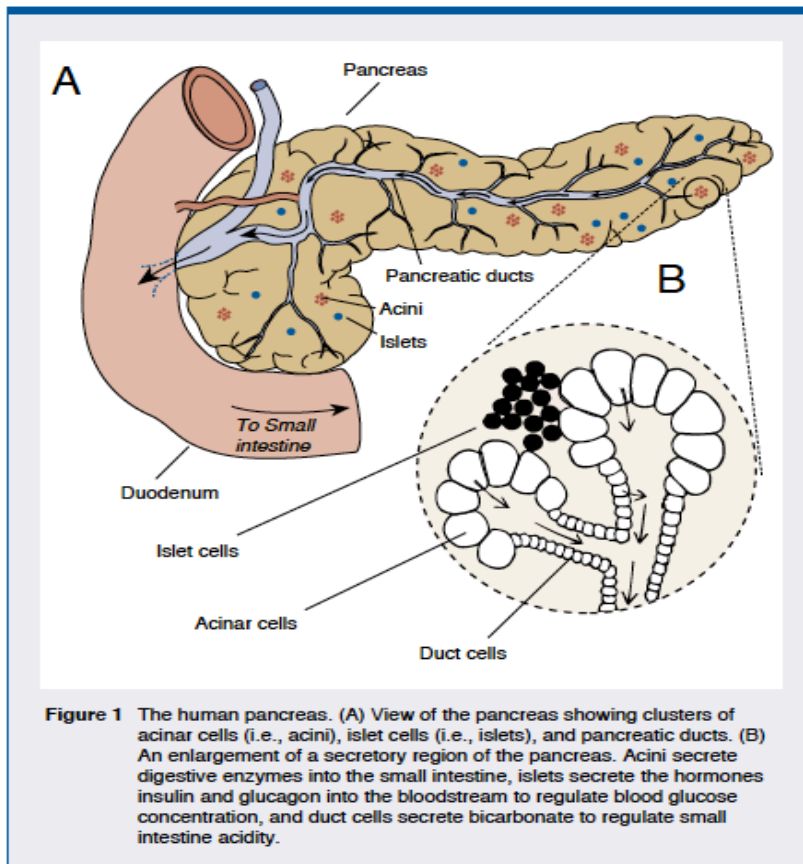


Figure 4 The pancreatic juice and the bile join each other in the common duct to be excreted in the duodenal lumen. In this figure gallstones obstruct the duct giving rise to the possibility of developing gallbladder en pancreas inflammation; one of the most common death causes in the world. Th sphincter of Oddi

(not mentioned) separates the duodenum from the common duct

The sphincter of Oddi, a circular muscular, impedes the exchange of duodenal content with the pancreas/liver duct. Cholecystokinin produced by duodenal gut lining cells produces relaxation of the sphincter, facilitating the entrance of bile and pancreatic juice in the duodenal lumen. Several factors influence the tonus of the sphincter (Barreto 2010):

- alcohol abuse
- high calorie diet (225 kcal/100 gram food, Dossus 2008)
- High carbohydrate diet
- Sympathetic hypertonus
- Insulin resistance
- Gallstones
- Gall inflammation
- Tobacco (DeBenedet 2009)

Situations with sphincter spasm has been related with the development of endocrine pancreas insufficiency and pancreatitis (Barreto 2010).

Function of pancreatic products

The pancreas is comprised of an endocrine and an exocrine portion. The endocrine portion consists of the islets of Langerhans, which are responsible for the secretion of insulin, glucagon, and somatostatin. Pancreatic exocrine tissues (the acini) produce digestive enzymes that are mixed with sodium bicarbonate from the ductules connecting the acini to the pancreatic duct. This pancreatic "juice" flows through the pancreatic duct, connecting with the hepatic duct, and ultimately emptying into the duodenum via the sphincter of Oddi. The digestive enzymes in the pancreatic juice break down carbohydrates, proteins, and fats (Table 1). Sodium bicarbonate neutralizes the acidic chyme that will make its way from the stomach to mix with the juice in the duodenum and start the enzyme-activating process.

Enzyme	Optimal pH Range	Action
Enterokinase (actually secreted in the small intestine)	5.2-6.0	Transforms trypsinogen into trypsin in duodenum
Proteolytic Enzymes: Trypsinogen (trypsin) Chymotrypsinogen (chymotrypsin) Carboxypolypeptidase Also various elastases and nucleases	7.9-9.7	Trypsin and chymotrypsin break down proteins into polypeptides and dipeptides; carboxypolypeptidase splits peptides into individual amino acids
Amylolytic Enzymes: Pancreatic amylase	6.7-7.2	Hydrolyzes starches, glycogen, and other carbohydrates (other than cellulose) into disaccharides and some trisaccharides
Lipolytic Enzymes: Lipase Phospholipase A1, A2 Esterase	8.0	Lipase hydrolyzes fats into fatty acids and monoglycerides; phospholipases split fatty acids from phospholipids; esterase hydrolyzes cholesterol esters

Table 1 The pancreatic juice products, their function and the optimal working pH (roxas 2008)

Problems can occur when there is a dysfunction in the ability of the pancreas to produce enzymes or the body's demand for enzymes exceeds the supply. This dysfunction can occur for a variety of reasons, including genetic predisposition, illness, injury/trauma, excessive exercise, aging, toxic exposure, or a combination thereof. A deficiency of pancreatic enzymes could potentially contribute to the development of numerous illnesses and degenerative conditions (Roxas 2008).

The normal chronology of pancreas enzyme production and activation; disorders based on fracture of chronology

Figure 5 shows the chronological production and activation of enzymes and other compounds involved in the digestion of normal food. At the time food reaches the duodenum it will be wrapped in gastric juice and gastric acid. The acid will lower duodenal pH which induces the production of secretine releasing peptide (SLP) by glandular pancreas cells. SLP will consequently stimulate S cells in the so called crypts of Lieberkühn in the duodenum, responsible for the production of secretin. At the same time cholecystokinin (CCK) is liberated by I-cells in the duodenal lining as a response of entering proteins and fat-rich chyme in the duodenum. Secretin induces bicarbonate (HCO_3) production by duct cells which neutralizes the gastric acid and optimizes the duodenal pH (8) for consequent enzyme activation. CCK receptors on acinar cells sense CCK and secrete chymotrypsin in the pancreatic duct which is then transported to the duodenal lumen. Chymotrypsin entering the duodenum will now be spliced and trypsin is liberated. The active trypsin is capable of hydrolizing peptides and thus produce amino acids which can be absorbed. Trypsin further activates other

digestive enzymes such as pre-amylases and pre-lipases which become carbohydrate and fat digesting enzymes. Proteins, carbohydrates and fat are converted in respectively amino acids, monosaccharides and fatty acids by this pathway making food available for the human body (figure 5).

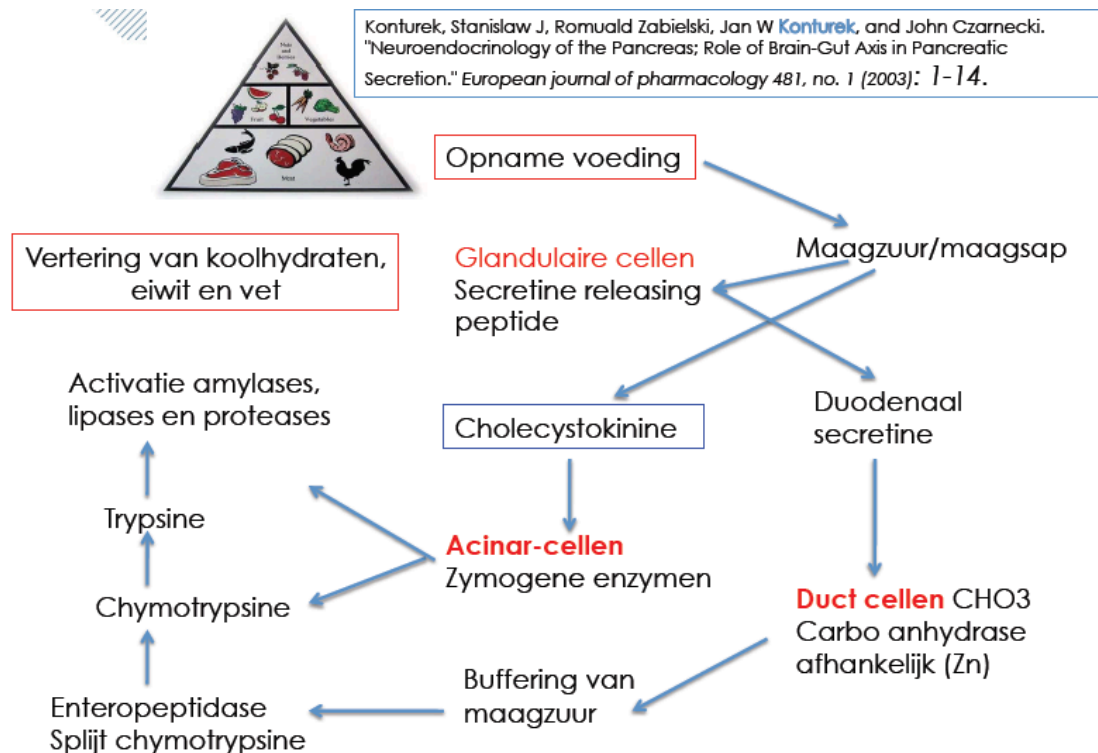


Figure 5 The chronology of production and activation of pancreatic enzymes during digestion of normal food

The activated pancreas enzymes are gradually degraded by deconjugated bilirubin which develops through the deconjugating capacity of another enzyme called beta-glucuronidase (β -GCD); an enzyme normally released by the gut mucosa and certain bacteria belonging to the normal microbiota of the human gut. Free deconjugated bilirubin (in contrast with the conjugated form) can be considered as the mayor protective compound of gut lining against the possible damaging effect of active proteases and lipases in parts of the gut where they not should be active (Qin 2002). Beta-glucuronidase is produced in high amounts in the healthy large intestine by *Escherichia coli* and *Streptococcus pyogenes*, which can only do so in a relative acid environment (pH 4 – 5); An environment based on the production of lactic acid by bifidobacteria (Qin 2007).

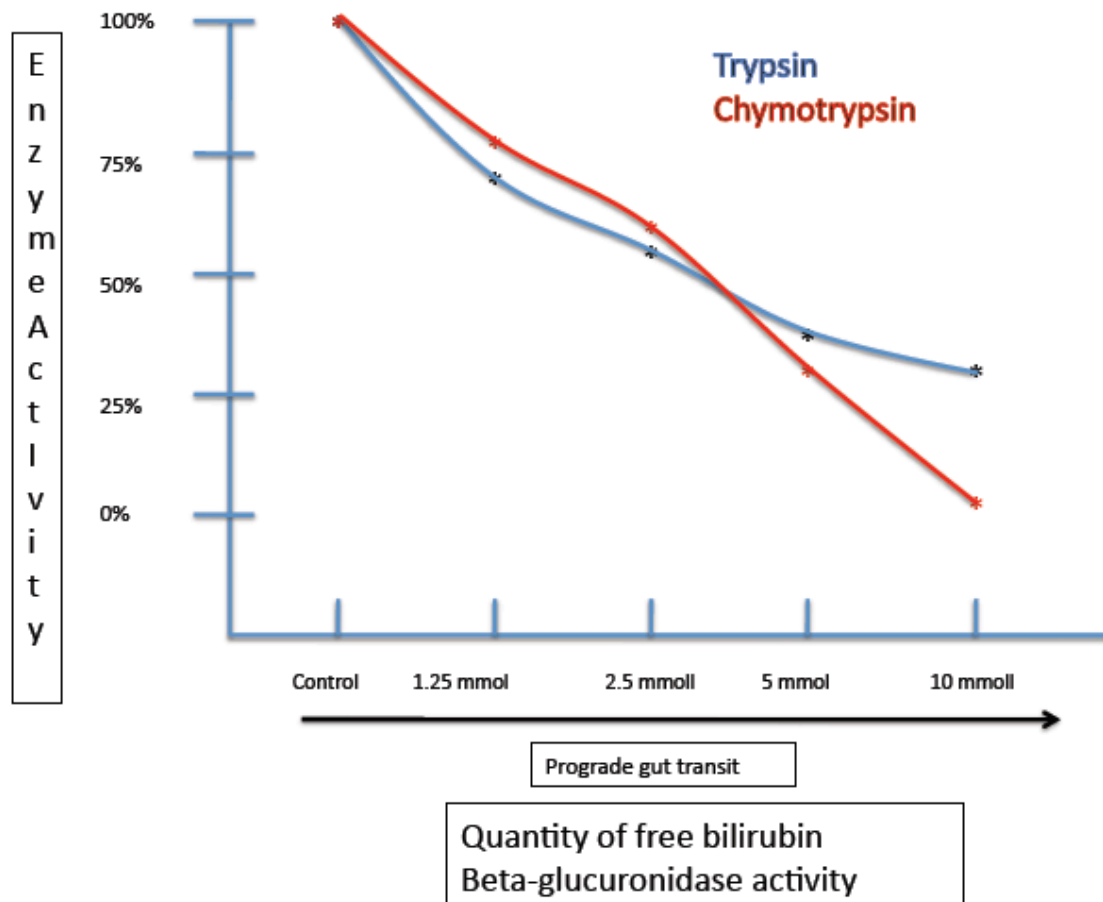


Figure 6 The inhibiting capacity of bilirubin compared with biliverdin. The increasing beta-glucuronidase activity in distal parts of the gut is responsible for the deconjugation of bilirubin, producing free active bilirubin and break-down capacity of activated pancreatic enzymes (adapted from Qin 2007)

Figure 6 shows that trypsin and chymotrypsin are significantly inhibited by free bilirubin, but not conjugated bilirubin or biliverdin (not showed). The nature of this inhibition and its physiological relevance were further explored for trypsin. Important is the fact that the inhibition is non-competitive, suggesting that free bilirubin can inactivate the enzyme. The effect of free bilirubin on protein digestion by trypsin was further investigated using chymotrypsinogen as the substrate. Bilirubin (10 mmol/l) showed 61% inhibition for the proteolytic activation of chymotrypsinogen A to chymotrypsin in a system containing 1 mg/ml trypsin and 1 mg/ml chymotrypsinogen for 30 min. Digestive proteases are inhibited by free bilirubin but not conjugated bilirubin. As bilirubin is secreted from the bile to the lumen mainly in the conjugated form, the digestion of dietary proteins in the upper small intestine would proceed smoothly. Deconjugation of bilirubin by beta-glucuronidase from the mucosal cells would form a protective layer on the surface of the gut. A more dramatic deconjugation of bilirubin by the high amounts of beta-glucuronidase from gut bacteria would further cause a prompt and effective inactivation of these digestive proteases in the lower intestine. Here we can see the wonderful design of nature that turns a waste byproduct into a precious treasure. The

amount of digestive proteases secreted by the pancreas largely depends on the amount of protein in the diet.

This would provide an explanation for the observation that bilirubin-predominant species tend to be carnivores or omnivores, while biliverdin-predominant species tend to be herbivores. Large amounts of bilirubin exist in the bile of cats, dogs, opossums, armadillos, alligators, African clawed toads, bullfrogs, mudpuppies, sharks (spiny dogfish), small skates, trout, goosefish, perch and humans, while biliverdin is the main bile pigment of rabbits, nutrias (rodents that eat water plants), sloths (leaf eaters), birds and tilapia (fish that eat algae).

Heme oxygenase catalyzes heme (from hemoglobin, cytochrom enzymes, cyclo-oxygenase) in biliverdin, which is further metabolized in bilirubin by biliverdin reductase. This happens in animals (including homo sapiens) which ingest a high amount of proteins and animal fat (carnivores). Heme oxygenase is produced by the so called vitagenes which are under control of indirect anti-oxidants such as curcumin (in turmeric root), resveratrol (in grapes, chocolat) and alliicin (in garlic). These substances are recognized for their protecting effect of the digestive system probably through upregulation of the production of (free) bilirubin (Calabrese 2006).

Evidence in vitro and vivo shows that deficiency of beta-glucuronidase and the subsequent lack of free bilirubin can be responsible for the development of irritable bowel syndrome (IBS), colitis ulcerosa (CU) and morbus Crohn (MC, Qin 2007). A meta-anaylisis about the use of probiotics with a high concentration of bifidus bacteria and lactobacillus showed a positive effect for probiotics in people suffering from IBS, UC and MC (Sang 2010). The proposed mechanisms for this positive effect are:

- recovering of the relationship between physiological bacteria and pathogenes
- restauration of immune tolerance
- increased production of beta-glucuronidase and free bilirubin, degradating possible ulcerating proteases in the large gut

Carbon anhydrase, expressed in duct cells of the pancreas and responsible for the production of bicarbonate, is dependent on nutritional zinc intake and absorbtion (Lukaski 2005). The mayor role of bicarbonate in the duodenum is to optimize pH, making pancreatic enzymes capable of executing their digestive role (figure 8 and table 1). Carbon anhydrase is a zinc dependent enzyme (figure 7).

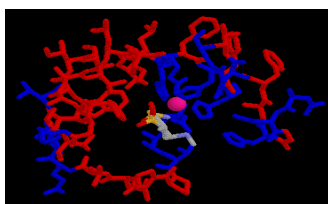
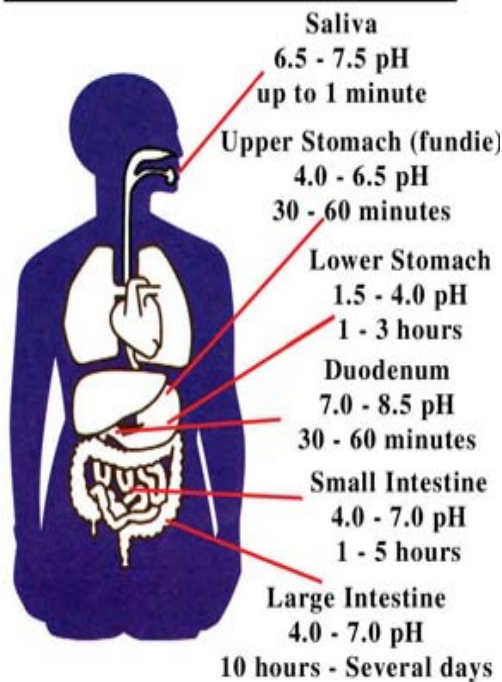


Figure 7 Carbon anhydrase, the most important enzyme for pH regulation not only in the digestive tract but also in the rest of the body including kidney nephrons and brain, contain in the centre of the molecule a zinc ion

The Human Digestive Tract pH Range Chart



The diagram illustrates the average time food spends in each part of the digestive system along with the average pH.

Figure 8 The average time food spends in each part of the digestive system related with average/optimal pH. The basic environment of the duodenum is necessary for optimal function of pancreatic enzymes (see table 1).

Zinc deficiency, a pandemic situation, has been related with carbon anhydrase insufficiency in multiple investigations (Lusaski 2005, Komai 2000) and is recognized as one of the mayor nutritional causes of diseases in developed and developing countries (www.who.int/whr/2002/chapter4/en/index3.html) One of the most valuable measurements for zinc deficiency is the preferred salt-taste test (figure 9, Komai 2000). This test, developed in rodents, shows a decreased oral salt sensibility when zin is deficient. A test which is also validated in humans (Stewart-Knox 2005).

Zinc supplementation can recover salt-sensibility through upregulation of carbon anhydrase production (Prasad 1998).

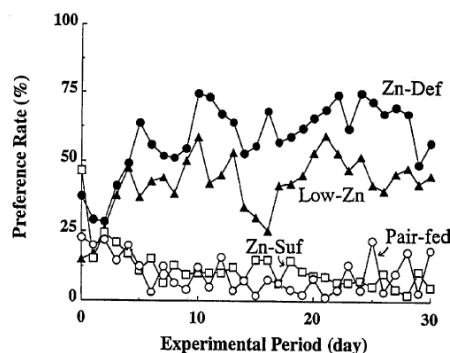


Figure 9 Preferred Salt-taste related with zinc deficiency (Komai 2000)

Zinc deficiency rate differ from 6 – 73% in selected countries and is often neglected as mayor cause of pathologies and disorders such as growth retardation, male hypogonadism, neuro-sensory changes (abnormal dark adaptation and changes in taste acuity), delayed wound healing, abnormal immune functions, and impaired cognitive functions, all of them reversible with zinc supplementation (Prasad 1998). A mild deficiency of zinc in pregnant women is associated with increased maternal morbidity, abnormal taste sensation, prolonged gestation, inefficient labor, atonic bleeding, and increased risks to the fetus.

Another mentioned enzyme in the digestive cascade is enteropeptidase. Enteropeptidase (synonym: enterokinase) was discovered, by N. P. Schepovalnikow in 1899, as a factor that is contained in the duodenum and that is capable of activating pancreatic juice to digest fibrin. Enteropeptidase acts as a sequence-specific protease activating trypsinogen by cleaving off an inhibitory portion. Trypsin, in turn, releases chymotrypsin, carboxypeptidases, elastases, and also lipases from their inactive pancreatic precursors. Intestinal activation of pancreatic precursors is the physiologic mechanism preventing the damage that proteases would cause if they were active within the pancreatic-duct system. Consequently, protein digestion is expected to be largely dependent on enteropeptidase activity. Enteropeptidase is exclusively expressed in the brush border of the proximal small intestine. Recently, enteropeptidase has been reported to be activated from an inactive precursor (proenteropeptidase) by duodenase, a newly discovered serine protease expressed in the duodenum (Holzinger 2002). Enteropeptidase deficiency is not a common disorder and needs no further explanation.

The exocrine pancreas insufficiency; etiology and central vagal mechanisms; the role of stress in pancreatic function

Exocrine pancreas insufficiency (EPI) is a syndrome characterized by a lack of active pancreatic enzymes in the duodenal lumen. It is a mayor consequence of primary pancreatic diseases such as chronic pancreatitis, cystic fibrosis, acute pancreatitis, pancreatic cancer and secundary pancreas disorders including celiac disease, morbus Crohn, lactose malabsorbtion and gastrointestinal – pancreatic surgical resection (Dominguez-Muñoz 2007). Exocrine pancreas insufficiency syndrome (EPI) can be caused by a variety of etiological factors. The most investigated factors are genetical ones, relating recurrent EPI with cystic fibrosis and the Schwachman-Diamond syndrome. The EPI syndrome in these disorders are very frequent and results of different human trials concerning the efficacy of use of pancreatic enzyme formulas make this intervention evidence based (Graff 2010).

Alcohol misuse, tobaco, micronutrient deficiency, high carbohydrate diet, high calorie diet, mayor intake of legumes and cereals, exercise deficit and exercise abundance are factors related with EPI in animal and in human studies (Braganza 2010, Barreto 2010, Taylor 2010, Dominguez-Muñoz 2007). The mentioned factors include the mayor intake of legumes (such as soy) and cereals as possible causal factors of EPI. Studies published already in the nineties and eighties of last century showed that cereal fibers and so called protease-inhibitors in legumes are able to inhibit the production and activation

of pancreatic enzymes (Hendrick 1991, Jacobs 1983, Dunaif 1981). The scientific excellent cereal paper of Cordain (Cordain 1999) adds to the fiber influence of legumes and cereals, the effects of lectins, saponins and protease-inhibitors (such as Bowman-Birk factors in legumes and Kunitz factors in potato) on the exocrine pancreas.

EPI is normally characterized by steatorrhea (fatty steaky stool), flatulence, bad breath and inflammation of the upper part of the abdomen (Roxas 2008). Symptoms are due to deficient digestion of fats, proteins and carbohydrates. Lipases seem to be the most vulnerable in EPI (Dominguez-Muñoz 2007). This is the reason for the fact that people suffering from EPI almost always have steatorrhea.

EPI can develop in acute and chronic pancreatitis when secretion of the pancreatic juice is impeded by gallstones in the pancreatic duct or by spasm of the sphincter of Oddi (see page 5). One of the major causes of gallstone is high carbohydrate intake (HCHD). HCHD seems to diminish the volume of the gall-bladder, augment cholesterol-gallstone formation and increases the crystal mass (Mathur 2007).

The combined production of secretin and CCK activates the pancreas and opens the sphincter of Oddi through three pathways (Konturek 2003). The secretion starts almost immediately after the meal with three overlapping phases: cephalic, gastric, and intestinal phases, contributing, respectively, to about 20%, 10%, and 70% of the total postprandial response to a meal. The postprandial phases, especially the cephalic phase, have been attributed mainly to vagal stimulation, with the efferent cholinergic nerves releasing acetylcholine in the pancreas and GRP-releasing neurons releasing gastrin from antral G-cells. It, in turn, stimulates acinar cells via CCK2 receptors. This cephalic phase can be induced by sham feeding in dogs or modified sham feeding in humans, as well as by insulin hypoglycemia or 2-deoxy-D glucose glucocytopenia, which stimulates the bulbar vagal centers with subsequent cholinergic excitation of exocrine pancreas, and GRPergic release of gastrin, which contributes to the activation of pancreatic acinar cells. Blocking vagal activity reduces the bicarbonate production by over 50%, which means that not only acinar cells are under vagal control, but duct cells as well. During the intestinal phase, the major role has been attributed to CCK and secretin, released from endocrine I and S-cells by protein and fat digestion products and by gastric acid entering the duodenum, respectively, but the relative contribution of these hormones and their potentiating interaction on postprandial pancreatic secretion has not been fully elucidated. There is little doubt that CCK plays a crucial role in the overall stimulation of pancreatic secretion as documented by the rise in plasma CCK level and the inhibitory effect of blockade of CCK1 receptors on this secretion, but its major pathways of action appear not to be endocrine, as was proposed in the past, but neural, involving the sensory receptors at afferent nerves and long vagovagal reflexes or short enteropancreatic reflexes, as depicted in figure 10, (Konturek 2003)

CCK appears to affect, through the same neural pathway, not only pancreatic secretion, but also bile secretion and gall bladder contraction as well as gastric emptying and pancreatic regeneration (growth).

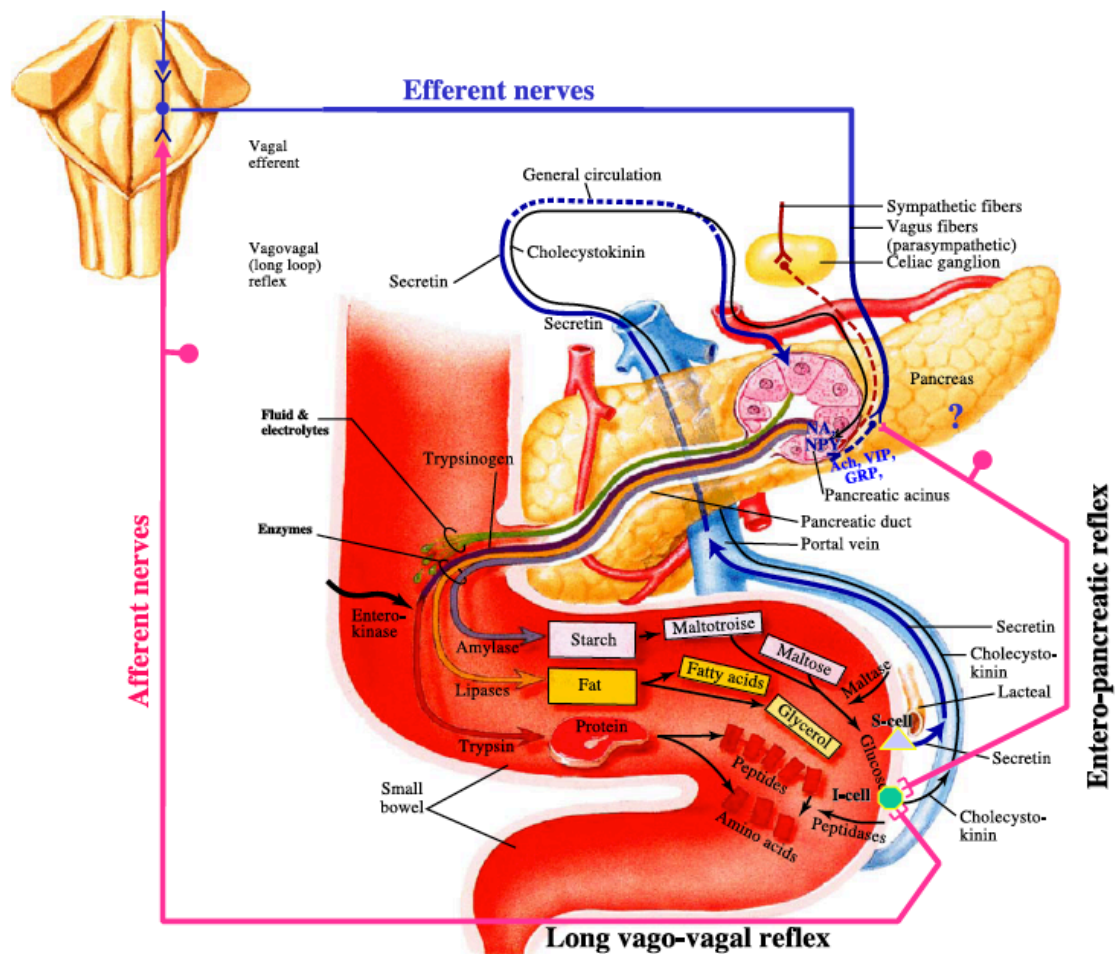


Figure 10 The overall regulation of exocrine pancreatic function through three different pathways; local duodenal liberation of CCK and secretin, stimulation via gastric juice and three, through vagal activity and acetylcholine release in the exocrine pancreas (Konturek 2003).

The exocrine pancreas, controlled by these three pathways, influences and is influenced by the endocrine pancreas which produces insulin, glucagon and somatostatin. In consequence of the close anatomical and functional links between the exocrine and endocrine pancreas, any disease affecting one of these parts will inevitably affect the other. Pancreatic conditions which might cause diabetes mellitus include acute and chronic pancreatitis, pancreatic surgery, cystic fibrosis and pancreatic cancer. The development of diabetes greatly influences the prognosis and quality of life of patients with exocrine pancreatic diseases. It may cause life threatening complications, such as hypoglycemia, due to the lack of glucagon and the impaired absorption of nutrients, or the micro- and macrovascular complications may impair the organ functions. Diabetes mellitus is an independent risk factor of mortality in those with exocrine pancreatic diseases. The treatment of pancreatic diabetes, a distinct metabolic and clinical form of diabetes, requires special knowledge. Diet and pancreatic enzyme replacement therapy, together with substances which improve insulin sensitivity may be sufficient in the early stages. Oral antidiabetic drugs are not recommended. If the diet proves inadequate to reach the glycemic goals, insulin treatment with multiple injections is

required. Impairments of the exocrine pancreatic function and morphology in diabetic patients are frequent and well known. Atrophy of the exocrine tissue may be caused by the lack of trophic insulin, whereas pancreatic fibrosis can result from activation of stellate cells by hyperglycemia, or from microangiopathy and neuropathy. The regulation of the exocrine pancreatic function is also damaged because of the impaired effect of islet hormones. In the event of a proven impairment of the pancreatic exocrine function in diabetes mellitus, pancreatic enzyme replacement therapy is indicated. This may improve the nutritional condition of the patient and decrease the metabolic instability (Czako 2009). Normal insulin seems to increase the production of pancreatic enzymes postprandial. Hyperinsulinemia (part of the metabolic syndrome) and hyperglycemia inhibit the release of secretin and CCK which can lead to severe lack of activated pancreatic enzymes, maldigestion and malabsorption (Pap 2004). People with acute or chronic pancreatitis express a higher activity of amylase enzymes, leading to a faster digestion of polysaccharides and a secular increase in blood glucose. The resulting chronic hyperglycemia seems to exhaust beta cells of the pancreas with a subsequent loss of insulin signalling. Insulin is necessary for pancreas regeneration after an pancreatic insult leading to pancreatitis, which means that a lack of insulin could impede pancreas recovery, produce multiple organ disorder, multiple organ failure and in the end death (Pap 2004).

Figure 11 shows the possible interaction between diabetes and pancreatitis; a situation which can be considered a devils vicious circle.

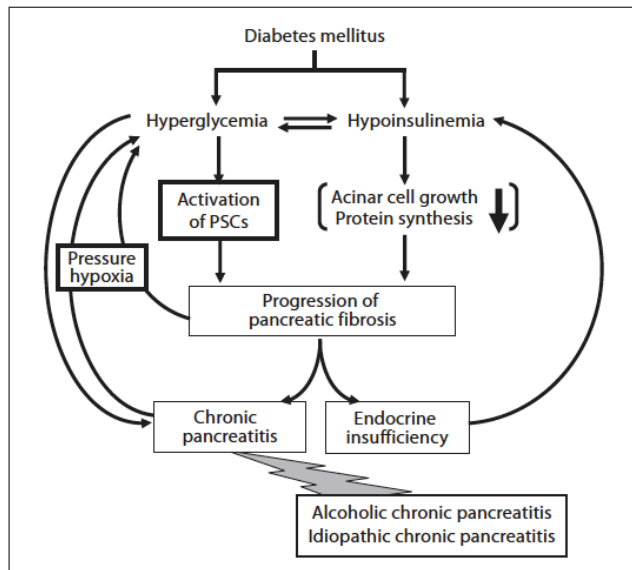


Figure 11. The interaction between DM and pancreatitis; a vicious circle (Czako 2009)

Table 2 shows the overall influence from different states of insulin on exocrine pancreatic function. Therapy of EPI should therefore not only regulate exocrine function but also the endocrine function of the pancreas (Lam 1999, Lam 1999^a, Lam 1997, Berry 1996).

• Hypo-insulinemia - Atrophy from the pancreas - Steatosis from acinar cells - Loss of CCK receptors • Insulin resistance - Decrease of CHO3 production - Decrease of CCK production - Decrease of vagal tonus • Hyperglycemia - Decrease of CHO3 - Decrease of CCK and basal pancreatic enzyme production
--

Table 2 The effect of different amounts of insulin and glucose on the exocrine pancreas function

Exocrine pancreas function is influenced by insulin through two pathways; the insulino-acinar pathway (Konturek 2003) and the pathway involving the central nervous system (Pruimboom 2005). Paradigmatic thinking has ruled medical thinking about interactions between the endocrine pancreas, the liver and the exocrine pancreas for decades. A non-inhibited liver will normally produce glucose output in the bloodstream. Postprandial pancreatic insulin is secreted in the portal vein and arrives for the fully 100% in the liver where neoglucogenesis is inhibited for just 20%. Non-used insulin reaches arterial blood through which it enters the brain. Insulin will activate anorexigenic neurons in the hypothalamus. These neurons are connected with and activate the nucleus tractus solitarius, which in turn activates the motoneurons of the nervus vagus. Efferents from these motoneurons innervate the liver and the pancreas, where they respectively inhibit neoglucogenesis (for the resting 80%) and induce secretion of pancreatic juice of the exocrine part (figure 12). Insulin resistance and fatty liver (NAFLD and AFLD) disease can disturb the function of this so called pancreas-liver-brain axis (Lustig 2006). Deficiency of central insulin signalling decreases activity of the vagus motoneurons; liver neoglucogenesis will be desinhibited, pancreatic output of enzymes decreased and EPI will be a logical consequence. The final conclusion is that chronic insulin resistance can be considered exocrine pancreas toxic through direct effects (insulino-acinar connection) and through long vagal reflex deficiencies. Probiotics, omega 3 fatty acids, curcumin and silybum extracts should be considered as first choice treatment for fatty liver disease, insulin resistance and restoration of the normal function of the pancreas-liver-brain axis (Masterton 2010, Esposito 2009, Solga 2008)

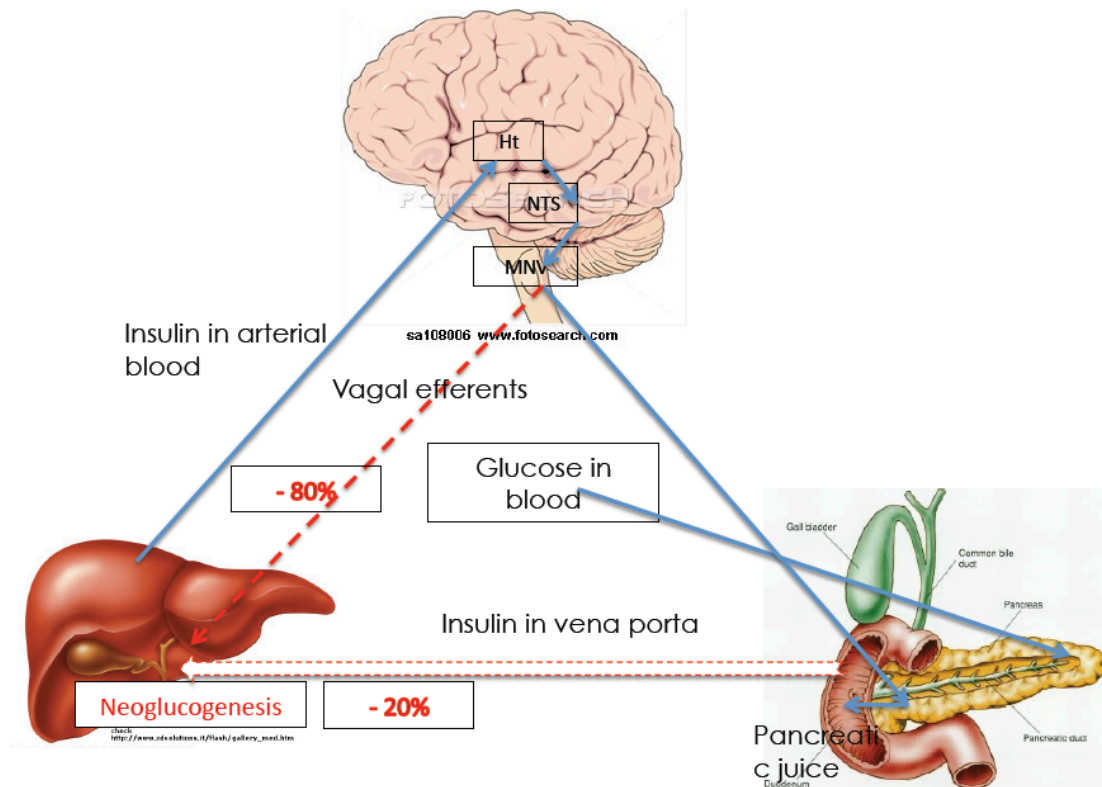


Figure 12 The pancreas, liver, brain axis. Explanation see text
Ht = hypothalamus, NTS = nucleus tractus solitarius, MNV = motoneurons of the nervus vagus

Pancreatitis

Acute and chronic pancreatitis belong to the diseases with the highest morbidity (Saluja 2007). Although there still exist a huge gap in our understanding of pancreatitis, some mechanisms are considered current opinion. Risk factors such as smoking, alcohol abuse, high calorie diet, but also several chemicals (e.g. pesticides, Barreto 2010, Braganza 2010) are able to overstimulate the exocrine pancreas and at the same time producing sphincter of Oddi spasm. The consequence is that pancreatic enzymes are not excreted in the duodenum lumen and stay in the pancreatic duct or in the acinar cells. Activation by a lysosomal enzyme called cathepsin beta can actually activate trypsin in the pancreas itself, producing activation of proteases, lipases and amylases in acinar cells, through which these cells will be damaged. The damaged cells attract neighbouring immune cells which infiltrate the pancreas and produce pro-inflammatory cytokines (IL1beta, TNF, IL6). The pancreas will now suffer a inflammation which can lead to multiple organ disorder, multiple organ failure and death (figure 13, Saluja 2007).

Pancreatic enzyme therapy seems to be the only valuable intervention together with withdrawal of alcohol, low carbohydrate diet, rest, direct and indirect antioxidants (Lieb 2009, Bhardwaj 2009). Candidates are selenium, vitamin C, vitamin E and cystein.

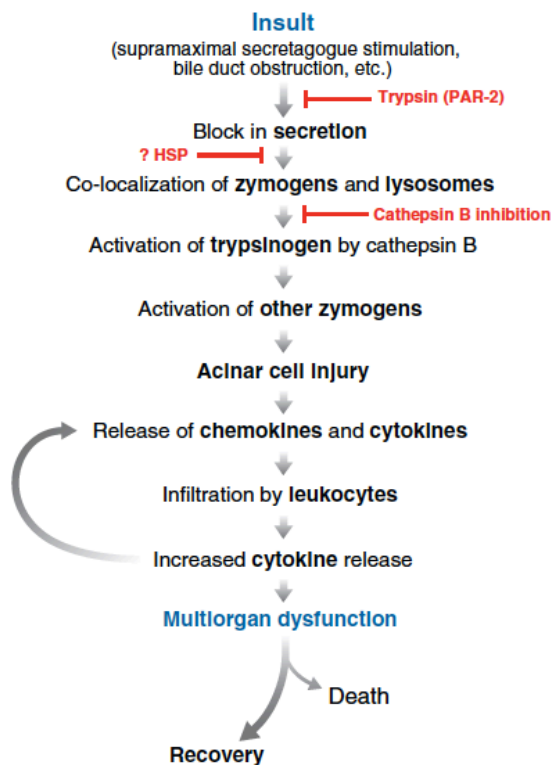


Figure 13 The development of acute and chronic pancreatitis (see text)

The clinical use of pancreatic enzymes

Exocrine Pancreas Insufficiency is a frequent disorder which can exist as a primary disease and a secondary pathology of disorders like cystic fibrosis and NAFLD. Therapy for pancreatic exocrine insufficiency is based on oral administration of exogenous pancreatic enzymes. In addition, dietary modifications have classically played an important role that should probably be reconsidered. Indications for therapy, the role of dietary modifications, the basis and critical aspects of enzyme substitution therapy, factors inhibiting normalization of fat digestion despite correct enzyme substitution therapy, ways to improve the efficacy of enzyme therapy, and future developments are discussed in the last part of this seminar text.

Major indications

People suffering from primary EPI show symptoms such as steatorrhea, abdominal cramps, taste deficiency, abdominal swelling, nutrient intolerance and general malaise. Treatment should be based on oral pancreatic enzymes, probiotics and fat soluble vitamins such as vitamin D, vitamin A and vitamin E (Cavelot 2006). Omega 3 fatty acids are needed for recovering of pancreas lipase transport and need to be supplemented.

Secondary EPI has to be treated as primary; pancreas function disorders can be responsible for lack of body energy up to 20% (of basal metabolic rate of 1600 kcal = 320 kcal/24 hours, Dominguez-Muñoz 2007). This can lead to multiple organ disorder, involving organs such as the liver and the kidneys. Pancreatic enzymes have been proven to be effective in diseases such as (Roxas 2008, Dominguez Muñoz 2007, Dominguez-Muñoz in press):

- pancreatic carcinoma
- Primary EPI
- Celiac disease
- Lactose intolerance
- Systemic disease
- IBS, morbus Crohn, colitis ulcerosa
- NAFLD

The dosing of oral pancreas enzymes is based on the amount of lipase in the supplement. Lipase is the most unstable pancreatic enzyme during gastrointestinal transit most probably due to the high sensitivity of pancreatic lipase to proteolysis and acidic pH. Due to proteolytic degradation, most amylase activity and more than 20% of trypsin activity but only 1% of lipase activity produced by the pancreas and secreted into the duodenum after a pure carbohydrate meal, are still present within the terminal ileum. Lipase also suffers irreversible inactivation at acidic pH, which is frequently present within the duodenum and jejunum in patients with pancreatic exocrine insufficiency due to low pancreatic bicarbonate secretion. In patients with pancreatic exocrine insufficiency, the reduced luminal action of pancreatic amylase and proteases is compensated for by salivary amylase, intestinal glycosidase, colonic flora, gastric pepsin, and intestinal peptidases. However, it has been generally accepted that digestive action of pancreatic lipase is hardly compensated by extrapancreatic mechanisms.

Many people suffer from helicobacter pylori and pH disorders, which means that oral enzyme therapy efficacy could be less than expected. If so, dosing should be raised and anti-acids (such as magnesium) should be added to the treatment.

Oral pancreatic enzyme therapy can be very effective and relieve a great variety of disorders. If the initial dosing has not been efficient, dosing should be doubled or tripled. After 2 weeks of treatment symptoms should be significantly less. Non-responding patients should be tested on bacterial overgrowth and possibly a carcinogenic process.

Conclusion

The exocrine pancreas, producing pancreatic enzymes and carbon anhydrase, plays a central role in maintaining human health by digesting food and making nutrients available for the body. Disorders of the exocrine pancreas are frequent and can be primary (caused by alcohol abuse, high calorie diet) or secondary to other pathologies (cystic fibrosis, celiac disease). Disturbances of exocrine function influence the endocrine pancreas and viceversa. Insulin protects the exocrine pancreas and is responsible for pancreas regeneration. Disorders of insulin signalling can cause (severe) malfunction of the exocrine pancreas, multiple organ failure and death.

Exocrine pancreas insufficiency is often not recognized while the incidence of people suffering from this disorder increases continuously. EPI is characterized by steatorrhea, abdominal swelling and cramps, bad breath and flatulence.

Lipase deficiency, the most vulnerable enzyme of the total pancreatic juice, is responsible for the majority of symptoms. Lipase deficiency further causes malabsorption of fat soluble vitamins (vitamin A, D, E) and omega 3 fatty

acids.

Gallstones are considered one of the most frequent etiological factors for EPI. High calorie and high carbohydrate diet are causal for gallstones. Gallstones can block the sphincter of Oddi through which pancreatic juice and bile should be excreted in the duodenal lumen. Obstruction can lead to acute and chronic pancreatitis and is considered one of the most frequent detach causes in developing and developed countries. Pancreatic enzymes have to be inactivated during gut travelling by free bilirubin. Free bilirubin is formed through activation of mucosal and bacterial produced beta-glucuronidase. A lack of this enzyme can cause IBS, CU and MC; one of the mayor causes of beta-glucuronidase deficiency is the intake of saccharin (Qin 2002).

Treatment with oral pancreatic enzymes have been proven effective in a wide range of disorders and pathologies, including acute/chronic pancreatis, pancreatic surgery, EPI, celiac disease, irritable bowel syndrome, colitis, morbus Crohn, lactose intolerance, trauma and systemic disease. Dosis depends on the reaction of the patient. Doubling or tripling of the initial dosis can be necessary.

Literature

- Barreto SG**, Gino T.P. Saccone Alcohol-induced acute pancreatitis: The 'critical mass' concept. *Medical Hypotheses* xxx (2010) xxx-xxx
- Berry SM**, Fink AS. Insulin inhibits secretin stimulated pancreatic bicarbonate output by a dosedependent neurally mediated mechanism. *Am J Physiol* 1996; 270:G163-170.
- Bhardwaj**, Payal, Pramod Kumar Garg, Subir Kumar Maulik, Anoop Saraya, Rakesh Kumar Tandon, and Subrat Kumar Acharya. "A Randomized Controlled Trial of Antioxidant Supplementation for Pain Relief in Patients with Chronic Pancreatitis." *Gastroenterology* 136, no. 1 (2009): doi:10.1053/j.gastro.2008.09.028.
- Braganza J**, Dormandi. Micronutrient Therapy for Chronic Pancreatitis: Rationale and Impact *J Pancreas (Online)* 2010 Mar 5; 11(2):99-112.
- Cavalot F**, Katia Bonomo, Elisa Fiora, Elisa Bacillo, Paola Salacone, Massimo Chirio, Ezio Gaiamariella Trovati. Does Pancreatic Elastase-1 in Stools Predict Steatorrhea in Type 1 Diabetes? *Diabetes Care*, VOLUME 29, NUMBER 3, MARCH 2006 (3): 719-721
- Czakó L**, Péter Hegyi, Zoltán Rakonczay, Jr. Tibor Wittmann Makoto Otsuki. Interactions between the Endocrine and Exocrine Pancreas and Their Clinical Relevance. *Pancreatology* 2009;9:351-359
- DeBenedet A**, T. Raghunathan, J. Wing, E. Wamsteker, M. Dimagno. Alcohol Use and Cigarette Smoking as Risk Factors for Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis. *Clinical Gastroenterology and Hepatology*, 2009, Volume 7, Issue 3, Pages 353-358.e4
- Cordain L**. Cereal Grains: Humanity's Double-Edged Sword Simopoulos AP (ed): *Evolutionary Aspects of Nutrition and Health. Diet, Exercise, Genetics and Chronic Disease*. World Rev Nutr Diet. Basel, Karger, 1999, vol 84, pp 19-73
- Dominguez-Muñoz, JE** . Pancreatic Enzyme Therapy for Pancreatic Exocrine Insufficiency. *Current Gastroenterology Reports* 2007, 9:116-122
- Domínguez-Muñoz JE**, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M: 13C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol*, in press.
- Dossus L**, Kaaks R. Nutrition, metabolic factors and cancer risk. *Best Practice & Research Clinical Endocrinology & Metabolism*. Vol. 22, No. 4, pp. 551-571, 2008
- Dunaif B**, Schneeman G. The effect of dietary fiber on human pancreatic enzyme activity in vitro. *The American Journal of Clinical Nutrition*, 1981, 34: 1034-1035
- Esposito E**, Iacono A, Bianco G, Autore G, Cuzzocrea S, Vajro Probiotics reduce the inflammatory response induced by a high-fat diet in the liver of young rats. *J Nutr*. 2009 May;139(5):905-11. Epub 2009 Mar 25
- Graff**, McNamara J, Royall J, Caras S, Forssmann K. Safety and Tolerability of a New Formulation of Pancrelipase Delayed-Release Capsules (CREON(R)) in Children Under Seven Years of Age with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis: An Open-Label, Multicentre, Single-Treatment-Arm Study. *Clin Drug Investig*. 2010;30(6):351-64
- Hendrick JA**, Tadahiyo Tadokoro, Curt Emenhiser, Owe Nienaber, and Owen R. Fennema. Various Dietary Fibers Have Different Effects on Lipase-Catalyzed Hydrolysis of Tributyrin in Vitro. *The American Journal of Nutrition* 1991

Holzinger A, Esther M. Maier, Cornelius Bu"ck, Peter U. Mayerhofer, Matthias Kappler, James C. Haworth, Stanley P. Moroz, Hans-Beat Hadorn, J. Evan Sadler, and Adelbert A. Roscher. Mutations in the Proenteropeptidase Gene Are the Molecular Cause of Congenital Enteropeptidase Deficiency. *Am. J. Hum. Genet.* 70:20–25, 2002

Jacobs LR. The American Journal of Clinical Nutrition 1983; 37: 954-960

Jaworek J, et al. Melatonin as modulator of pancreatic enzyme and pancreas protector. *Journal of Physiology and Pharmacology*, 2007, 58. Suppl. 6: 65-80

Kamhi, Ellen, **Ph.D., RN**, HNC (2007). *Alternative Medicine Magazine's Definitive Guide to Weight Loss*. Celestial Arts. pp. 14. ISBN 1587612593. "Ornithine is converted by bowel bacteria into a toxic substance called putrescine, which in turn degrades into polyamines, such as spermadine, spermine, and cadaverine (literally meaning "the essence of dead cadavers").

Komai M, Tomoko Gotoa, Hitoshi Suzukib, Tomohiko Takedaa and Yuji Furukawa. Zinc deficiency and taste dysfunction; Contribution of carbonic anhydrase, a zinc-metalloenzyme, to normal taste sensation *BioFactors* 12 (2000) 65–70

Konturek SJ, Romuald Zabielskib, Jan W. Konturekc, John Czarnecki. Neuroendocrinology of the pancreas; role of brain–gut axis in pancreatic secretion *European Journal of Pharmacology* 481 (2003) 1–14

Lam WF, Masclee AA, Souverijn JH, Lamers CB. Effect of acute hyperglycemia on basal, secretin and secretin + cholecystokinin stimulated exocrine pancreatic secretion in humans. *Life Sci* 1999; 64:617-626.

Lam WF, Muller ES, Souverijn JH, et al. Effect of acute hyperglycaemia on basal and fat-induced exocrine pancreatic secretion in humans. *Clin Sci (Lond)* 1997; 93:573-580.

Lam WF, Gielkens HA, Coenraad M, et al. Effect of insulin and glucose on basal and cholecystokinin-stimulated exocrine pancreatic secretion in humans. *Pancreas* 1999; 18:252-8.

Leja-Szpakb A, j. Jaworekb, r. Tomaszewskaa, k. Nawrotb, J. Boniorb, M. Kotb , M. Palonekb, J. Stachuraa, A. Czuprynab, S. J. Kontureka, W.W. Pawlika. Melatonin precursor, l-tryptophan protects the pancreas from development of acute pancreatitis through the central site of action. *Journal of Physiology and Pharmacology* 2004, 55, 1: 239-254

Lewis, Robert Alan (1998). *Lewis' Dictionary of Toxicology*. CRC Press. pp. 212

Lieb, J G, and C E Forsmark. "Pain and Chronic Pancreatitis." *Alimentary pharmacology & therapeutics* (2009)doi:10.1111/j.1365-2036

Lukaski HR. Low dietary zinc decreases erythrocyte carbonic anhydrase activities and impairs cardiorespiratory function in men during exercise. *Am J Clin Nutr* 2005;81:1045–51.

Lustig RH. Childhood obesity: behavioral aberration or biochemical drive? Reinterpreting the First Law of Thermodynamics. *Nature Clinical Practice endocrinology & metabolism*, 2006, 2 (8): 447 - 458

Masterton GS, Plevris JN, Hayes PC. Review article: omega-3 fatty acids - a promising novel therapy for non-alcoholic fatty liver disease • *Aliment Pharmacol Ther.* 2010 Apr;31(7):679-92.

Mathur, Abhishek MD, Marine Megan, BS, Hayder H. Al-Azzawi, MD, Debao Lu, MD, Deborah A. Swartz -Basile, PhD, Attila Nakeeb, MD, and Henry A. Pitt, MD. High dietary carbohydrates decrease gallbladder volume and enhance cholesterol crystal formation. *Surgery* 2007;141:654-9

Masamune Atsushi,* Takashi Watanabe,* Kazuhiro Kikuta, Kennichi Satoh, and

Tooru Shimosegawa. NADPH oxidase plays a crucial role in the activation of pancreatic stellate cells *Am J Physiol Gastrointest Liver Physiol* 294: G99–G108, 2008

Pap A. Effects of insulin and glucose metabolism on pancreatic exocrine function. *Int J Diabetes & Metabolism* (2004) 12: 30-34

Prasad SA. Zinc Deficiency in Humans: A Neglected Problem. *Journal of the American College of Nutrition*, Vol. 17, No. 6, 542–543 (1998)

Pruimboom, L. Eetstoornissen. *Van Nature* 2005, 1: 38 - 40

Roxas M. The role of enzyme supplementation in digestive disorders. *Alternative Medicine Review* Volume 13, Number 4 2008

Saluja AK, Markus M. Lerch, Phoebe A. Phillips, and Vikas Dudeja. Why Does Pancreatic Overstimulation Cause Pancreatitis? *Annu. Rev. Physiol.* 2007. 69:249–69

Sang LX, Bing Chang, Wen-Liang Zhang, Xiao-Mei Wu, Xiao-Hang Li, Min Jiang Remission induction and maintenance effect of probiotics on ulcerative colitis: A meta-analysis. *World J Gastroenterol* 2010; 16(15): 1908-1915

Solga SF, Buckley G, Clark JM, Horska A, Diehl AM. The effect of a probiotic on hepatic steatosis. *J Clin Gastroenterol.* 2008 Nov-Dec;42(10):1117-9

Stewart-Knox BJ *, EEA Simpson, H Parr, G Rae, A Polito, F Intorre, N Meunier, M Andriollo-Sanchez, JM O'Connor, C Coudray and JJ Strain. Zinc status and taste acuity in older Europeans: the ZENITH study. *European Journal of Clinical Nutrition* (2005) 59, Suppl 2, S31–S36

Taylor, J R, T B Gardner, A K Waljee, M J Dimagno, and P S Schoenfeld. "Systematic Review: Efficacy and Safety of Pancreatic Enzyme Supplements for Exocrine Pancreatic Insufficiency." *Alimentary pharmacology & therapeutics* 31, no. 1 (2010): doi:10.1111/j.1365-2036.2009.04157.x.

Qin X. Inactivation of Digestive Proteases: Another Mechanism That Probiotics May Have Conferred a Protection. *The American Journal of Gastroenterology* (2007) 102, 2109; doi:10.1111/j.1572

Qin XF. Inactivation of digestive proteases by biliverdin the possible evolutionary driving force for bilirubin or deconjugated bilirubin predominance in animals: *Gut* 2007 56: 1641-1642

Qin XF. Impaired inactivation of digestive proteases by deconjugated bilirubin: The possible mechanism for inflammatory bowel disease. *Medical Hypotheses* (2002) 59(2), 159–163