Experimental evidence of obesity as a risk factor for severe acute pancreatitis

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Abstract

The incidence of acute pancreatitis, an inflammation of the pancreas, is increasing worldwide. Pancreatic injury is mild in 80%–90% of patients who recover without complications. The remaining patients may develop a severe disease with local complications such as acinar cell necrosis, abscess and remote organ injury including lung injury. The early prediction of the severity of the disease is an important goal for physicians in management of patients with acute pancreatitis in order to optimize the therapy and to prevent organ dysfunction and local complications. For that purpose, multiple clinical scale scores have been applied to patients with acute pancreatitis. Recently, a new problem has emerged: the increased severity of the disease in obese patients. However, the mechanisms by which obesity increases the severity of acute pancreatitis are unclear. Several hypotheses have been suggested: (1) obese patients have an increased inflammation within the pancreas; (2) obese patients have an increased accumulation of fat within and around the pancreas where necrosis is often located; (3) increase in both peri- and intra-pancreatic fat and inflammatory cells explain the high incidence of pancreatic inflammation and necrosis in obese patients; (4) hepatic dysfunction associated with obesity might enhance the systemic inflammatory response by altering the detoxification of inflammatory mediators; and (5) ventilation/perfusion mismatch leading to hypoxia associated with a low pancreatic flow might reduce the pancreatic oxygenation and further enhance pancreatic injury. Recent experimental investigations also show an increased mortality and morbidity in obese rodents with acute pancreatitis and the implication of the adipokines leptin and adiponectin. Such models are important to investigate whether the inflammatory response of the disease is enhanced by obesity. It is exciting to speculate that manipulation of the adipokine milieu has the potential to influence the severity of acute pancreatitis.

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Key words: Acute pancreatitis; Obesity; Adiponectin; Leptin

INTRODUCTION

The incidence of acute pancreatitis is increasing worldwide[1]. Most episodes of acute pancreatitis are mild and self-limiting, requiring only a short hospitalization[2]. However, 10% of the patients (with a significant proportion of obese patients) develop a severe disease with local and extra-pancreatic complications characterized by early development and persistence of hypovolemia and multiple organ dysfunction[3,4]. Following the initial pancreatic edema, necrosis is the most severe local complication. The patchy areas of nonviable parenchyma are initially sterile but may be infected by bacteria originating mostly from the gut whose permeability increases during the disease. The most important extra-pancreatic complication is lung injury with a high incidence in severe
pancreatitis, ranging from 15% to 55% [5]. The severity of pulmonary complications varies greatly from mild hypoxemia without clinical or radiological abnormalities to severe acute respiratory distress syndrome. Two peaks of pulmonary complications were observed during the early phase of severe acute pancreatitis, the first peak being described upon admission with new radiological abnormalities by day 5 [6]. Hepatic injury is mild in acute pancreatitis but may participate in the propagation of inflammation from pancreas to other organs, mostly lungs [7,8].

### INCREASED SEVERITY OF ACUTE PANCREATITIS IN OBESE PATIENTS

Several clinical investigations showed that obesity increases the severity of the disease by favoring local complications within the pancreas and injuries in remote organs as well as by increasing the mortality rate [9,10]. Obesity increases the incidence of early shock, renal and pulmonary failure [11] and extends the hospital stay [12]. However, other studies have questioned such findings [11,12].

The mechanisms by which obesity increases the severity of acute pancreatitis is unclear, but one hypothesis might be that obese patients have an increased inflammatory response within the pancreas [11,12]. In the study by Sempere et al. [13], among 85 consecutive patients with acute pancreatitis, 74% had a mild disease while the remaining patients were severely ill. Serum concentrations of interleukin-1α (IL-1α), IL-1 receptor antagonist (IL-1-ra), IL-6, IL-8, IL-10 and IL-12p70 were significantly increased in patients with acute pancreatitis as compared with volunteers, and the concentrations were significantly higher in obese patients. One explanation is that obesity per se induces a chronic inflammatory state [11,13]. A second hypothesis is that obese patients have an increased accumulation of fat within and around the pancreas where necrosis is often located. The risk of pancreatic infection and inflammation would be proportional to the increased amount of peri-pancreatic fat. Accordingly, patients with intra-pancreatic fat are more prone to develop local complications following pancreatic surgery [11,24]. Interestingly, cytokine expression in fat tissue is higher in obese than in lean subjects [21].

In obese patients, the cytokine expression is also higher in visceral than in subcutaneous fat, cytokines being produced mainly by macrophages located in the stromavascular fraction of fat tissues [21]. Thus, increase in both peri- and intra-pancreatic fat and presence of inflammatory cells in adipose tissues might explain the high incidence of pancreatic inflammation and necrosis in obese patients. Weight loss improves the inflammatory profile of fat tissue with an increased expression of anti-inflammatory factors such as IL-10 and IL.1-ra [21]. Similarly, in inflammatory bowel diseases, visceral fat is also a source of inflammatory signal [22,23]. A third hypothesis is that pancreatic microcirculation is lower in obese than in non-obese patients, which increases the risk of ischemic injury and subsequent local infections. Moreover, obese patients might be immunodeficient, a condition that increases the risk of local infections [24]. Finally, because obesity restricts the movement of the chest wall and diaphragm, inspiratory capacity of obese patients is reduced. Ventilation/perfusion mismatch may lead to hypoxemia that, in conjunction with low blood flow, further decreases tissue oxygenation to the pancreas.

### BRIEF OVERVIEW OF THE PATHOPHYSIOLOGY OF ACUTE PANCREATITIS

Although controversial, most observers believe that acute pancreatitis is caused by the dysregulated activation of trypsin within pancreatic acinar cells. Enzyme activation within the pancreas leads to autodigestion of the gland followed by local inflammation. The main factors that trigger the acute disease are pancreatic hyperstimulation (mainly observed in experimental models), gallstones and alcohol abuse in humans. Acute pancreatitis occurs when intracellular protective mechanisms designed to prevent trypsinogen activation or reduce trypsin activity are decreased or overwhelmed. Following the activation of trypsinogen into active trypsin within acinar cells, numerous enzymes such as elastase and phospholipase A2, as well as complement and kinin systems, are activated [25] (Figures 1 and 2). Additionally, inflammation is initiated with local production of mediators such as tumor necrosis factor-α (TNF-α), IL-1 and IL-8 from neutrophils, macrophages and lymphocytes [26,27]. In addition to these events, activation of endothelial cells permits the transendothelial migration of leukocytes that release other harmful mediators [28].

Thus, regardless of the initial trigger of the disease, the severity of pancreatic damage is related to the injury of acinar cells and to the activation of inflammatory and endothelial cells. Local complications such as acinar cell necrosis may develop and injury in remote organs (lungs) results from the release of numerous mediators from the pancreas or extrapancreatic organs (Figure 1).

### EXPERIMENTAL PANCREATITIS, OBESITY, ADIPOCYTES AND INFLAMMATION

Fat tissues are likely to contribute to the increased inflammation in obese rodents. Thus, adipokines secreted by adipocytes are potent regulators of the inflammatory response, leptin being considered as a pro-inflammatory adipokine, while adiponectin functions as an anti-inflammatory mediator (Table 1). Adipose tissues also produce cytokines that participate in the inflammatory response of obesity and organ dysfunction. Thus, pancreatic necrosis following intrapancreatic duct injection of taurocholic cid (TA) was similar in obese fa/fa rats and lean...
fa/+ rats, but the survival was lower in obese rats[30]. The pancreatic expression of TNF-α and IL-6 was higher in obese than in lean rats while IL-10 expression was lower[31]. TNF-α expression was also higher in liver and lungs from obese rats. Moreover, obese rats with acute pancreatitis had steatohepatitis while livers in lean rats were normal. Thus, dysregulation between inflammatory and anti-inflammatory mediators in obese rats is an important issue to explain the increased severity of the disease. These investigators also determined whether high-fat feeding vs. normal diet may influence the severity of the disease. These investigators also determined whether high-fat feeding vs. normal diet may influence the severity of the disease.

Body weight doubles in fa/fa rats. Restricted feeding does not modify the occurrence of obesity. The obesity is associated with an increase in the number and size of adipocytes. These rats have hyperlipidemia and hypercholesterolemia. The pancreas weight is similar in fa/fa and fa/+ rats but, according to the increased body weight of fa/fa rats, the ratio between pancreas and body weight is lower in fa/fa rats[30]. Of note, amylase content is lower in fa/fa than fa/+ rats and treatment with ciglitazone that increases the insulin sensitivity partially prevents this low pancreatic amylase content[31]. Administration of cholecystokinin (CCK) is known to decrease food intake but the obese rats have a higher threshold than lean rats for this effect[30]. Moreover, the exocrine response to cerulein and carbachol is decreased in acini isolated from fa/fa rats while the response to secretin or vasoactive intestinal peptide is identical[30,31]. When CCK is incubated in isolated acini, less amylase is secreted in fa/fa rats than in lean rats[32]. In fa/fa and fa/+ rats, the expression of CCKα and CCKβ receptors is unknown. To overcome the absence of effects on the receptor, circulating leptin expression is increased. Leptin mRNA is detected in adipose tissue but not in pancreas, lungs, or liver[30]. The expression of leptin decreases gradually from epididymal to retroperitoneal, subcutaneous, and interscapular brown adipose tissue. In isolated adipocytes, leptin mRNA expression is also significantly higher in fa/fa than in control rats. Finally, TNF-α protein expression in adipose (perirenal and epididymal) tissues is similar in both strains[33].

The severity of acute pancreatitis has been investigated in other experimental models of obesity, such as ob/ob and db/db mice. Both mice are congenitally obese but manifest this phenotype via different mechanisms. Ob/ob mice have a spontaneous mutation of the ob (leptin) gene and produce no leptin while db/db mice have a spontaneous mutation of the leptin receptor and have increased circulating concentrations of leptin. Ob/ob mice may reach three times the normal weight of wild-type mice. Obesity is characterized by an increase in the number and size of adipocytes. Although hyperphagia contributes to obesity, excess of weight is also

### Table 1 Severity of acute pancreatitis and adipokines

| Adipokine  | Effects                                      | Final effect |
|-----------|----------------------------------------------|--------------|
| Leptin    | ↑ TNF-α                                      | Pro-inflammatory |
|           | ↑ Chemotaxis                                  |              |
|           | ↑ Neutrophil activation                       |              |
|           | ↑ IL-6                                       |              |
|           | ↑ T-cell proliferation                        |              |
| Adiponectin| ↓ TNF-α                                      | Anti-inflammatory |
|           | ↓ IL-6                                       |              |
|           | ↓ Phagocytosis                                |              |
|           | ↑ IL-10                                      |              |
|           | ↑ IL-1RA                                     |              |

Adiponectin may be considered as an anti-inflammatory compound whereas leptin acts as a proinflammatory mediator. Both adipokines may influence the severity of pancreatitis.
observed with a restrictive diet sufficient for lean mice. Interestingly, ob/ob mice have impaired pulmonary bacterial clearance of Streptococcus pneumoniae and increased pulmonary concentrations of cytokines\[40\]. Ob/ob mice are less hyperglycemic than db/db mice. Moreover, in pancreas from ob/ob mice, content of triglycerides, free fatty acids, cholesterol and total fat is higher than in lean mice\[46\]. Serum concentrations of IL-1 and TNF-α are also increased.

In a model of acute pancreatitis induced by two injections of IL-12 plus IL-18, all ob/ob mice died within 48 h while all wild-type mice survived\[41\]. To differentiate the contribution of obesity or leptin deficiency to the severity of the disease, a group of ab/ab mice had leptin replacement therapy (obesity with normal leptin). Interestingly, this group had severe acute pancreatitis, suggesting that obesity per se and not leptin deficiency was responsible for the severe acute pancreatitis. Moreover, the authors generated “slim” ab/ob mice that had a less severe acute pancreatitis, reinforcing the finding that obesity rather than leptin deficiency was responsible for the severity of acute pancreatitis. In another study, three experimental groups received injections of cerulein: C57BL/6J (lean), ob/ob (obese mice with leptin deficiency), and db/db (obese mice with leptin receptor deficiency and increased circulating leptin) mice\[42\]. Both ab/ab and db/db mice developed a significantly more severe disease than wild-type lean mice associated with an increase in pancreatic inflammatory cytokines. Finally, in patients matched for body mass index, the circulating leptin did not correlate with the severity of the disease\[43\]. These studies confirmed the feeling that leptin production does not relate to the severity of acute pancreatitis.

However, the role of leptin in acute pancreatitis remains puzzling (Table 1). In pancreatitis induced by cerulein injections in lean rats, serum leptin concentrations increased by 12 h and remained high for 36 h\[44\]. When a more severe disease was induced (arginine model), leptin concentrations were high at 12 and 24 h but were similar at 48 h in both experimental models. Thus, in lean rodents, the serum concentrations of leptin increase in acute pancreatitis but no relationship is found between severity of the disease and circulating leptin concentrations. To further investigate the role of leptin in the severity of the disease, rats with acute pancreatitis were treated with leptin (10 μg/kg ip) after the last cerulein injection\[45\]. Leptin treatment increased the survival rate and the severity of acute pancreatitis. Moreo-, the anti-inflammatory adipokine adiponectin has also been investigated in experimental pancreatitis. Adiponectin decreases in obesity and inversely mirrors the severity of experimental pancreatitis\[46\]. Adiponectin acts through the receptors AdipoR1 and AdipoR2. Both receptors are expressed in rodent pancreas but AdipoR1 expression is significantly decreased in the pancreas of ob/ob and db/db mice as compared with wild-type lean mice\[46\]. To investigate the role of adiponectin in the severity of acute pancreatitis, adiponectin knockout (APN-KO) and wild type mice were injected with a low dose of cerulein two weeks after normal or high-fat-diet\[47\]. Whereas APN-KO mice fed a high-fat-diet treated with cerulein developed pancreatic damage and inflammation, wild-type mice did not. Finally, adenovirus-mediated over-expression of adiponectin attenuates the severity of acute pancreatitis in APN-KO mice\[47\]. All these data clearly demonstrate that adiponectin plays a protective role in the cerulein model of acute pancreatitis.

### INTERACTION OF CHOLECYTOKININ, DIGESTIVE PROENZYMES AND LEPTIN

Confusion on the protective or deleterious role of leptin in acute experimental pancreatitis may also arise from the fact that a crosstalk between CCK and leptin pathways is observed in acinar cells. CCK is produced in endocrine cells present in the mucosa of the small intestine following the ingestion of proteins and fat. CCK stimulates the contraction of gallbladder and relaxes the sphincter of Oddi (facilitating bile secretion into the intestine) and stimulates pancreatic secretion by acinar cells either by a direct effect or through acetylcholine released by the vagus nerve that possesses receptors for CCK. CCK also represents a proliferative hormone for the pancreas and by delaying gastric emptying induces satiety. Leptin, produced and secreted from white adipocytes, regulates food intake and energy consumption\[48\]. Intravenous administration of leptin diminishes the postprandial pancreatic secretions\[49\]. Administration of leptin does not affect the volume of bile and pancreatic juice while the protein and trypsin output is reduced\[49\]. The effect of leptin becomes stronger when protein and trypsin secretions are stimulated by CCK. In contrast, leptin does not affect basal and CCK-8-stimulated amylose release in pancreatic acini, suggesting that leptin does not act directly on pancreatic acinar cells but inhibits the secretion of pancreatic enzymes through CCK-vagal-dependent mechanism\[49\]. In contrast to the intravenous administration, intraduodenal leptin administration to fasted rats increases pancreatic protein and amylase secretions, this effect being related to the stimulation of CCK release through activation of duodeno-pancreatic reflexes\[49\].

Otsuka Long-Evans Tokushima Fatty (OLETF) rats are spontaneously diabetic rats with polyuria, polydipsia, hyperglycemia, mild obesity and diabetes\[51\]. These rats do not express the CCK-A receptor mRNA in pancreas. This lack of CCK-A receptors results in a reduced ability to produce nutrient-induced satiety signals which leads to increase in meal size, overall hyperphagia and obesity. Administration of increasing doses of CCK8 induced a biphasic dose-response curve of pancreatic juice and protein secretion in control Long-Evans Tokushima Otsuka (LETO) rats whereas the OLETF rats did not respond to CCK-8\[52\]. Cerulein injections induce acute

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pancreatitis in LETO rats but did not increase serum amylose or lipase activities in OLETF rats.

Finally, the rat pancreatic acinar tumor (AR42J) cell lines do express the leptin receptor[3]. The binding of leptin is specific to the leptin receptor and does not cross-react with CCK pathway. Leptin does not modify basal amylose release but inhibits amylose release stimulated by CCK. Leptin alone has no effect on intracellular Ca\(^{2+}\) mobilization but pre-treatment with leptin enhances the Ca\(^{2+}\) response to CCK. Thus, AR42J cells express a functional leptin receptor that modulates the action of CCK on Ca\(^{2+}\) mobilization and amylose release[3]. Relationship between enzyme release from acinar cells and signals of satiety such as leptin in lean and obese rodents are complex and further investigations are needed.

**CONCLUSION**

The prevalence of obesity has increased worldwide. Despite numerous clinical investigations, the precise mechanisms involved in the pathogenesis of acute pancreatitis remain elusive, and currently no specific medical therapy is available beyond general support. Investigating the mechanisms, by which acute pancreatitis develops from novel angles such as obesity, offers potentially new observations that may ultimately lead to the development of useful treatment. It is exciting to speculate that manipulation of the adipokine milieu has the potential to influence the severity of acute pancreatitis. Thus, investigations along these lines are warranted.

**REFERENCES**

1. Frey CF, Zhou H, Harvey DJ, White RH. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreaticitis in California, 1994-2001. Pancreas 2006; 33: 336-344
2. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008; 371: 143-152
3. Halonen KI, Pettilä V, Leppäniemi AK, Kemppainen EA, Povelakainen PA, Haapianen RK. Multiple organ dysfunction associated with severe acute pancreatitis. Crit Care Med 2002; 30: 1274-1279
4. Vincent JL, de Mendonça A, Cartraire F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on 'sepsis-related problems' of the European Society of Intensive Care Medicine. Crit Care Med 1996; 24: 1793-1800
5. Pastor CM, Matthay MA, Frossard JL. Pancreatitis-associated acute lung injury: new insights. Chest 2003; 124: 2341-2351
6. Berry AR, Taylor TV, Davies GC. Pulmonary function and fibrinogen metabolism in acute pancreatitis. Br J Surg 1981; 68: 870-873
7. Closa D, Bardaji M, Hotter G, Prats N, Gelpí E, Fernández-Cruz I, Roselló-Catafau J. Hepatic involvement in pancreatitis-induced lung damage. Am J Physiol 1996; 270: G6-G13
8. Folch-Puy E. Importance of the liver in systemic complications associated with acute pancreatitis: the role of Kupffer cells. J Pathol 2007; 211: 383-388
9. Martínez J, Sánchez-Payá J, Palazón JM, Suaizo-Barahona J, Robles-Díaz G, Pérez-Mateo M. Is obesity a risk factor in acute pancreatitis? A meta-analysis. Pancreatology 2004; 4: 42-48
10. Martínez J, Johnson CD, Sánchez-Payá J, de Madaria E, Robles-Díaz G, Pérez-Mateo M. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. Pancreatology 2006; 6: 206-209
11. Abu Hilal M, Armstrong T. The impact of obesity on the course and outcome of acute pancreatitis. Obes Surg 2008; 18: 326-328
12. Sempere L, Martínez J, de Madaria E, Lozano B, Sánchez-Paya J, Jover R, Perez-Mateo M. Obesity and fat distribution imply a greater systemic inflammatory response and a worse prognosis in acute pancreatitis. Pancreatology 2008; 8: 297-304
13. De Waele B, Vannierlo B, Van Nieuwenhove Y, Delvaux G. Impact of body overweight and class I, II and III obesity on the outcome of acute biliary pancreatitis. Pancreas 2006; 32: 343-345
14. Lanksch PG, Schirren CA. Increased body weight as a prognostic parameter for complications in the course of acute pancreatitis. Pancreas 1990; 5: 626-629
15. Blomgren KB, Sundström A, Steinbeck G, Wilholm BE. Obesity and treatment of diabetes with glyburide may both be risk factors for acute pancreatitis. Diabetes Care 2002; 25: 298-302
16. Stima D, Krznarić Zrnić I, Radic M, Zuvic-Butorac M. Is obesity a risk factor in acute pancreatitis? Dig Dis Sci 1998; 43: 2251-2254
17. Papachristou GI, Papachristou DJ, Avula H, Slivka A, Whitcomb DC. Obesity increases the severity of acute pancreatitis: performance of APACHE-O score and correlation with the inflammatory response. Pancreatology 2006; 6: 279-285
18. Ghanim H, Aljada A, Hofmeyer D, Syed T, Mohanty P, Dandona P. Circulating mononuclear cells in the obese are in a proinflammatory state. Circulation 2004; 110: 1564-1571
19. Pitt HA. Hepato-pancreato-biliary fat: the good, the bad and the ugly. HPB (Oxford) 2007; 9: 92-97
20. Clement K, Langin D. Regulation of inflammation-related genes in human adipose tissue. J Intern Med 2007; 262: 422-430
21. Gambero A, Maróstica M, Abdalaa Saaj MD, Pedrazzoli J Jr. Mesenteric adipose tissue alterations resulting from experimental reactivated colitis. Inflamm Bowel Dis 2007; 13: 1357-1364
22. Arulampalam V. Gastrointestinal inflammation: lessons from metabolic modulators. J Intern Med 2008; 236: 607-612
23. Lamara M, Marta A, Martínez JA. Obesity and immunocompetence. Eur J Clin Nutr 2002; 56 Suppl 3: S42-S45
24. Frossard JL, Hadengue A, Pastor CM. New serum markers for the detection of severe acute pancreatitis in humans. Am J Respir Crit Care Med 2001; 164: 162-170
25. Norman R, Fink GW, Franz MG. Acute pancreatitis induces intrapancreatic tumor necrosis factor gene expression. Arch Surg 1995; 130: 966-970
26. Glooor B, Todd KE, Lane JS, Rigberg DA, Reber HA. Mechanism of increased lung injury after acute pancreatitis in IL-10 knockout mice. J Surg Res 1998; 80: 110-114
27. Poch B, Gansauge F, Rau B, Wittel U, Gansauge S, Nüssler AK, Schoenberg M, Beger HG. The role of polymorphonuclear leukocytes and oxygen-derived free radicals in experimental acute pancreatitis: mediators of local destruction and activators of inflammation. FEMS Lett 1999; 461: 268-272
28. Segersvård R, Syltvå M, Herrington M, Larsson J, Perment J. Obesity increases the severity of acute experimental pancreatitis in the rat. Scand J Gastroenterol 2001; 36: 658-663
29. Segersvård R, Tsai JA, Herrington MK, Wang F. Obesity alters cytokine gene expression and promotes liver injury in rats with acute pancreatitis. Obesity (Silver Spring) 2008; 16: 23-28
30. Segersvård R, Syltvå M, Lemppinen M, Larsson J, Perment
J. Impact of chronic and acute high-fat feeding on acute experimental pancreatitis complicated by endotoxinemia. *Scand J Gastroenterol* 2004; 39: 74-80

32 Phillips MS, Liu Q, Hammond HA, Dunan V, Hey PJ, Caskey CJ, Hess JF. Leptin receptor missense mutation in the fatty Zucker rat. *Nat Genet* 1996; 13: 18-19

33 Noto A, Zahradka P, Ryz NR, Yurkova N, Xie Y, Taylor CG. Dietary conjugated linoleic acid preserves pancreatic function and reduces inflammatory markers in obese, insulin-resistant rats. *Metabolism* 2007; 56: 142-151

34 Trimble ER, Bruzzone R, Belin D. Insulin resistance is accompanied by impairment of amylase-gene expression in the exocrine pancreas of the obese Zucker rat. *Biochem J* 1986; 237: 807-812

35 McLaughlin CL, Peikin SR, Baile CA. Decreased pancreatic exocrine response to cholecystokinin in Zucker obese rats. *Am J Physiol* 1982; 242: G612-G619

36 Trimble ER, Bruzzone R. Abnormalities of caerulein- and carbamylcholine-stimulated pancreatic enzyme secretion in the obese Zucker rat. *Regul Pept* 1985; 11: 227-235

37 McLaughlin CL, Peikin SR, Baile CA. Decreased pancreatic CCK receptor binding and CCK-stimulated amylase release in Zucker obese rats. *Physiol Behav* 1984; 32: 961-965

38 Ogawa Y, Masuzaki H, Isse N, Okazaki T, Mori K, Shigemoto M, Satoh N, Tamura N, Hosoda K, Yoshimasa Y. Molecular cloning of rat obese cDNA and augmented gene expression in genetically obese Zucker fatty (fa/la) rats. *J Clin Invest* 1995; 96: 1647-1652

39 Hsu A, Aronoff DM, Phipps J, Goel D, Mancuso P. Leptin improves pulmonary bacterial clearance and survival in ob/ob mice during pneumococcal pneumonia. *Clin Exp Immunol* 2007; 150: 332-339

40 Mathur A, Marine M, Lu D, Swartz-Basile DA, Saxena R, Zyromski NJ, Pitt HA. Nonalcoholic fatty pancreas disease. *HPB (Oxford)* 2007; 9: 312-318

41 Sennello JA, Fayad R, Pini M, Gove ME, Ponemone V, Cabay RJ, Siegmund B, Dinarello CA, Fantuzzi G. Interleukin-18, together with interleukin-12, induces severe acute pancreatitis in obese but not in nonobese leptin-deficient mice. *Proc Natl Acad Sci USA* 2008; 105: 8858-8870

42 Zyromski NJ, Mathur A, Pitt HA, Lu D, Gripe JT, Walker JJ, Yancey K, Wade TE, Swartz-Basile DA. A murine model of obesity implicates the adipokine milieu in the pathogenesis of severe acute pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 2008; 295: G552-G558

43 Tuklainen E, Kylanpaa ML, Ebeling P, Kemppainen E, Puolakkainen P, Repo H. Leptin and adiponectin levels in acute pancreatitis. *Pancres* 2006; 32: 211-214

44 Kerem M, Bedirli A, Pasaoglu H, Unsal C, Yilmaz TU, Ofiuoglu E, Sahin TT. Role of ghrelin and leptin in predicting the severity of acute pancreatitis. *Dig Dis Sci* 2007; 52: 950-955

45 Gultekin FA, Kerem M, Tatlicioglu E, Aricioglu A, Unsal C, Bukan N. Leptin treatment ameliorates acute lung injury in rats with cerulein-induced acute pancreatitis. *World J Gastroenterol* 2007; 13: 2932-2938

46 Wade TE, Mathur A, Lu D, Swartz-Basile DA, Pitt HA, Zyromski NJ. Adiponectin receptor-1 expression is decreased in the pancreas of obese mice. *J Surg Res* 2009; 154: 78-84

47 Araki H, Nishihara T, Matsuda M, Fukuhara A, Kihara S, Funahashi T, Kataoka TR, Kamada Y, Kiyohara T, Tamura S, Hayashi N, Shimomura I. Adiponectin plays a protective role in caerulein-induced acute pancreatitis in mice fed a high-fat diet. *Gut* 2008; 57: 1431-1440

48 Frühbeck G. Intracellular signalling pathways activated by leptin. *Biochem J* 2006; 393: 7-20

49 Matyjek R, Herzig KH, Kato S, Zabielski R. Exogenous leptin inhibits the secretion of pancreatic juice via a duodenal CCK1-vagal-dependent mechanism in anasthetized rats. *Regul Pept* 2003; 114: 15-20

50 Nawrot-Porabka K, Jaworek J, Leja-Szpak A, Palonek M, Szklarczyk J, Konturek SJ, Pawlik WW. Leptin is able to stimulate pancreatic enzyme secretion via activation of duodeno-pancreatic reflex and CCK release. *J Physiol Pharmacol* 2004; 55 Suppl 2: 47-57

51 Moran TH. Unraveling the obesity of OLETF rats. *Physiol Behav* 2008; 94: 71-78

52 Tachibana I, Akiyama T, Kanagawa K, Shiohara H, Furumi K, Watanabe N, Otsuki M. Defect in pancreatic exocrine and endocrine response to CCK in genetically diabetic OLETF rats. *Am J Physiol* 1996; 270: G730-G737

53 Harris DM, Flannigan KL, Go VL, Wu SV. Regulation of cholecystokinin-mediated amylase secretion by leptin in rat pancreatic acinar tumor cell line AR42J. *Pancreas* 1999; 19: 224-230

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