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TOPIC HIGHLIGHT

Asbjørn Mohr Drewes, MD, PhD, DMSc, Professor, *Series Editor*

Animal models of pancreatitis: Can it be translated to human pain study?

Jing-Bo Zhao, Dong-Hua Liao, Thomas Dahl Nissen

Jing-Bo Zhao, Dong-Hua Liao, Mech-Sense, Department of Gastroenterology and Surgery, Aalborg University Hospital, DK 9000 Aalborg, Denmark
Jing-Bo Zhao, Dong-Hua Liao, Institute of Clinical Medicine, Aarhus University, DK 8200 Aarhus N, Denmark
Jing-Bo Zhao, Dong-Hua Liao, The College of Bioengineering, Chongqing University, Chongqing 400016, China
Thomas Dahl Nissen, Biomedical Research Laboratory, Aalborg University Hospital, DK 9000 Aalborg, Denmark
Author contributions: Zhao JB, Liao DH and Nissen TD designed, drafted, revised and finally approved this paper.
Correspondence to: Jing-Bo Zhao, MD, PhD, Mech-Sense, Department of Gastroenterology and Surgery, Aalborg University Hospital, Sdr. Skovvej 15, DK 9000 Aalborg, Denmark. jz@rn.dk
Telephone: +45-9-9326907 Fax: +45-9-9326801
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Abstract

Chronic pancreatitis affects many individuals around the world, and the study of the underlying mechanisms leading to better treatment possibilities are important tasks. Therefore, animal models are needed to illustrate the basic study of pancreatitis. Recently, animal models of acute and chronic pancreatitis have been thoroughly reviewed, but few reviews address the important aspect on the translation of animal studies to human studies. It is well known that pancreatitis is associated with epigastric pain, but the understanding regarding to mechanisms and appropriate treatment of this pain is still unclear. Using animal models to study pancreatitis associated visceral pain is difficult, however, these types of models are a unique way to reveal the mechanisms behind pancreatitis associated visceral pain. In this review, the animal models of acute, chronic and un-common pancreatitis are briefly outlined and animal models related to pancreatitis associated visceral pain are also addressed.

Key words: Animal model; Pancreatitis; Visceral pain; Mechanism

Core tip: Choosing the right model of pancreatitis is difficult and the scientific rationale needs to be carefully considered. Furthermore, no model of pancreatitis parallels all classical symptoms and the question under investigation is of importance when choosing a model. One of the main symptoms of chronic pancreatitis is visceral pain and in order to improve the pain treatment and obtain more knowledge about the physiology behind the pancreatitis associated visceral pain, animal models of pancreatitis associated visceral pain are needed.

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INTRODUCTION

Pancreatitis represents a common disorder of the gastrointestinal tract. Acute pancreatitis (AP) has an incidence ranged from 4.9 to 35 per 100000 populations[1], whereas chronic pancreatitis (CP) has an incidence from 2.4 to 4.4 per 100000 populations[2]. The etiology of this disease is complex and so far a variety of environmental factors including alcohol abuse, nicotine habits, hereditary factors, efferent duct obstructions, immunological factors and rare metabolic factors have all been described. However,

the pathophysiology of AP and CP remains poorly defined[3]. As a result appropriate therapies are still limited, and prognosis has not improved to date, which is mainly due to the lack of a satisfactory animal model of pancreatitis[4,5].

It is well known that pancreatitis is associated with visceral pain, however, the understanding of pain signaling related to pancreatitis is poor[6]. In order to facilitate the development of new pharmaceutical treatments for AP and CP, characterization of the mediators and receptors or ion channels on the sensory nerve terminals and the pathways of the pain signaling are needed. Therefore, in this aspect, the animal models of pancreatitis are needed in parallel in order to explore the mechanism behind pancreatitis associated visceral pain, as this is difficult to study in humans.

In this review, we briefly outline the animal models of acute, chronic and un-common pancreatitis as well as animal models related to pancreatitis associated visceral pain.

ANIMAL MODELS OF ACUTE PANCREATITIS

AP is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood[7]. Other characteristics of AP include edema, acinar cell necrosis, hemorrhage, and severe inflammation of the pancreas. Severe AP may lead to systemic inflammatory response syndrome and multi-organ dysfunction syndrome, which account for the high mortality rates of AP[8,9]. As it is difficult to study AP in the clinic, animal studies are important in order to understand the pathogenesis of AP, however an AP model which is strictly comparable to human AP is still needed. The current animal models of AP have contributed to our knowledge of mechanisms involved in early cellular events, pathogenesis and pathophysiology of AP[10,11]. We have illustrated the summary of existing AP animal models in Table 1[12-59]. Details of different AP animal models including advantages, disadvantages and clinical relevance can be found in a recently published review[4]. From a methodological aspect, selecting the appropriate AP animal model depends on the objectives of each study as different animal models are targeted to different AP features. For developing the effective treatment for AP in the clinic, continued investigation of AP animal models are needed.

Table 1 Different animal models of acute pancreatitis

Methods	Models and examples
Non-invasive	Hormone-induced
	Acute caerulein pancreatitis of rats[12], mice[13], dogs[14], and syrian hamsters[15]
	Trinidadian scorpion toxin induced acute pancreatitis in dogs[16]
	Alcohol-induced: rats[17-19], cats[20] and dogs[21]
	Immune-mediated
	Ovalbumin in rabbit[22]
	Foreign serum in mice[23] and rat[24]
	Spontaneous model of autoimmune acute pancreatitis mice[25]
	Diet-induced: Fed a choline-deficient diet containing ethionine in mice[26]
	Gene knockout: Interleukin (IL)-1 and tumour necrosis factor-α[27], IL-6[28], IL-10[29], chemoattractant cytokine receptor-1[30], neurokinin-1 receptor[31], intercellular adhesion molecule 1 (ICAM-1)[32], metallothionein-1[33], cathepsin B[34], mouse a2-macroglobulin and murinoglobulin[35], complement factor C5a[36], granulocyte-macrophage colony-stimulating factor[37] and phospholipase A2[38]
	L-arginine-induced: Administration of a large dose of *L*-arginine in rats[39,40]
Invasive	Closed duodenal loop (CDL): Dog[41] and rat[42,43]
	Antegrade pancreatic duct perfusion: Cat[44] and rat[45]
	Various compounds infusion into the pancreatic duct: Rat[46] and dog[47]
	Combined intraductal glycodeoxycholic acid with intravenous caerulein: Rat[48]
	Vascular-induced
	Impairment of pancreatic circulation in dogs[49]
	To occlude pancreatic arteries in rats[50]
	Occlusion of pancreatic veins in dogs[51] and in rats[52]
	Complete but reversible ischaemia of the pancreas by occluding different arteries using microvascular clips: Rats[53] and canine[54]
	Duct ligation
	Ligating the distal bile duct at the level of the duodenum[55]
	Combined pancreatic duct ligation with the secretory stimulation, secretin in dogs[56]
	Combining duct ligation with both secretory stimulation and minimal arterial blood[57]
	Duct-ligated opossums models[58]
	Transient obstruction of the sphincter of Oddi (SO) in Australian brush tailed possums[59]

ANIMAL MODELS OF CHRONIC PANCREATITIS

A recently published review[5] has described the most frequently used and best established models for CP in animals. The majority of the animal models are rodent models, since mice and rats are easy to handle and there is a steadily increasing number of genetic models obtained by gene deletion or transgenic expression of genetic variants. In the same way for animal models of AP, the models of CP can be classified into noninvasive or nonsurgical models and invasive or surgical models. Table 2 summarizes different animal models of CP[60-100].

In the non-invasive models, repetitive caerulein injections are amongst the most widely used models. Firstly, caerulein injections are relatively easy to perform and show a high reliability and reproducibility. Secondly, other compounds mediating injury such as lipopolysaccharides or cyclosporin A can easily be added to the design. Thirdly, serial caerulein injections can be performed in transgenic or knockout animals. It is likely that there are dose and frequency dependency for caerulein. The most translational models include repetitive injections of *L*-arginine, which appears to produce CP similar to that in humans[70-72]. In this model, fibrotic tissues are progressively

Table 2 Different animal models of chronic pancreatitis

Methods	Models and examples
Non-invasive	Caerulein-induced Serial caerulein injections in mice[60] and rats[61] Combination of repetitive caerulein injections with toxins and other agents such as lipopolysaccharides[62], cyclosporin A[63], dibutyltin dichloride[64] and Alcohol[65-67] Intraperitoneal caerulein injections are administered in genetically transformed mice such as TRX-1 transgenic mice[68,69] Arginine-induced A single *L*-arginine injection in rat[70] Serial *L*-arginine injections[70-72] Alcohol feeding-induced: Lieber-DeCarli formula[73-76] Genetic models: Wistar Bonn/Kobori (WBN/Kob) rats[77-79]; R122H transgenic mice[80]; SPINK3-deficient (SPINK3-/-) mice[81]; CFTR-deficient (cftrm1UNC) mice[82] and CFTR(-/-) pigs[83]; Kif3a-deficient mice[84]; PERK-deficient (PERK-/-) mice[85]; Interleukin 1-β transgenic mice[86]
Invasive	Sodium taurocholate-induced: Retrograde infusion of sodium taurocholate (NaTc) into the pancreatic duct system of the rat[87] Oleic acid-induced: Retrograde infusion of oleic acid[72,88-91], viscous solution of zein[92], mixture of zein-oleic acid, or viscous solution consisting of zein-oleic acid-linoleic acid[93,94] into rat pancreatic duct Congestion of pancreatic fluid flow: Combination of transient stasis of pancreatic juice flow and mild pancreatic duct injury[95] Duct ligation model Ligation of the common bile duct close to the duodenum pancreatic tissue in dogs[96], mouse[97] and pigs[98] Incomplete pancreatic duct ligation in canine[99] Occlusion with two different tissue glues in the rat[100]

replaced with adipose tissue. Due to the high impact of alcohol consumption as a risk factor on the pathogenesis in human pancreatic diseases, alcohol has frequently been used to trigger CP in animal models[73,74]. However, it is still being considered whether a model for CP induced by alcohol alone is feasible or satisfactory. The combination of alcohol feeding with caerulein injections exacerbates the course of pancreatitis and consequently increases pancreatic fibrosis and the loss of parenchyma.

Genetic animal models of CP are suitable for different studies. It is well known that activation of trypsinogen is one of the key events in the early phase of pancreatitis, and therefore genetic abnormalities found in the trypsinogen gene and in its inhibitors might be of particular importance of which R122H transgenic mice[80] are a good example. Transgenic expression of the *R122H* mutation of murine trypsin 4 in the pancreas of mice led to progressive fibrosis and chronic inflammation of the pancreas. Repetitive inductions of experimental pancreatitis with supramaximal doses of cerulein resulted in extensive deposition of collagen in periacinar and perilobular spaces of this transgenic animal. However other genetic models might also help us to understand how CP develops[77-79,81,83-86,101].

Invasive animal models can also be used to induce CP. As an example, retrograde infusion of sodium taurocholate (NaTc) into the pancreatic duct[46] or intraductal infusion of NaTc[72] can generate pancreatitis, however the structure of the pancreatic tissue will return to an almost normal state after 14 d. Retrograde infusion of oleic acid[72,88-91], viscous solution of zein[92], a mixture of zein-oleic acid or a viscous solution consisting of zein-oleic acid-linoleic acid[93,94] into rat pancreatic duct will cause severe pancreatic atrophy with irregular fibrosis and fat replacement over a period of 6 mo. However, these models of pancreatitis appear quite distinct from CP in humans. As one factor alone is inadequate to cause persistent pancreatic injury, a combination of transient stasis of pancreatic juice flow and mild pancreatic duct injury is a well established and reliable method to generate CP in animal models[95]. It is well known that pancreatic ductal hypertension contributes to the pathogenesis of CP; therefore animal models can also be generated by complete obstruction of the pancreatic duct[96-98], incomplete pancreatic duct ligation[99] and occlusion with different tissue glues[100]. Yamamoto *et al*[102] developed an animal model with pancreatic ductal hypertension and demonstrated that this plays an important role in the onset and development of CP in rats. However, models for CP based on duct obstruction are not common and there is only a minority of studies examining the morphological and biochemical changes of the pancreas after duct ligation[41,103,104].

ANIMAL MODELS OF UN-COMMON PANCREATITIS

Un-common types of pancreatitis can include autoimmune pancreatitis (AIP), hereditary pancreatitis[105], groove pancreatitis[106], tropical pancreatitis, pancreatitis in ectopic or heterotopic pancreatic tissue, ascaris-induced pancreatitis, pancreatitis in cystic fibrosis, pancreas divisum, annular pancreas, pancreatic cancer manifesting as AP, and duodenal villous adenoma with pancreatitis. With exception of AIP and hereditary pancreatitis, no relevant animal models were found for other un-common pancreatitis. Furthermore, hereditary pancreatitis animal models were mentioned in the genetic animal models of CP above. Therefore only animal models of AIP are briefly introduced in this section.

To date, several animal models of AIP have been described. The first model involves the adoptive transfer of amylase-specific (an antigen mainly located in acinar cells) $CD4^+$ T cells and results in pancreatitis in naive syngenic recipient animals[107]. Notably, the histological lesions of this model mimic the lobulocentric inflammatory reaction in type 1 AIP. A model developed by immunization of neonatally thymectomized mice with CA (an antigen mainly located on the pancreatic epithelium) and later transfer of $CD4^+$ lymphocytes resulted in a duct-centric pattern of pancreatitis resembling type 2 AIP[108]. In another model, NTx-NFS/sld mice spontaneously developed sialoadenitis in which a-fodrin was involved as an autoantigen, as reported in some patients with Sjogren syndrome and AIP[109]. Transforming growth factor-β

(TGFβ) appears to be an important regulatory factor in maintaining immune homeostasis. Loss of TGFβ signalling contributes to AIP in TGFβ dominant negative mutant mice[110].

Recently two animal models for AIP were proposed. The WBN/Kob rat model, associated with congenital decreased peripheral Tregs spontaneously develops sialoadenitis, thyroiditis, sclerosing cholangitis and tubulointerstitial nephritis[111]. Although the target antigens remain unclear, $CD8^+$ cells may be the effector cell in this rat model[112]. Another recently described animal model of AIP is the Treg-deficient NOD mouse[113]. CD28KO mice spontaneously develop AIP that closely resembles the human disease[113]. More recently, Haruta *et al*[114] investigated the possible involvement of chronic, persistent exposure to avirulent bacteria in the pathogenesis of AIP using C57BL/6 mice.

Existing animal models for AIP have several limitations. In most models the disease is induced by adoptive transfer of autoreactive cells and/or antibodies rather than spontaneous development of the disease with identical antigen specificity. The distribution of lesions produced in animal models for AIP is also variable. This may be attributed to the diversity of target antigens, different methods of immune staining and different mouse strains. In addition, typical histopathological findings of AIP (*e.g.*, lymphoplasmacytic infiltration with fibrosis, obliterative phlebitis and GELs) are rarely observed in animal models. Thus, there is a need to develop spontaneous animal models with identical autoantigens and typical histopathological findings for AIP.

VISCERAL PAIN IN ANIMAL MODELS OF CHRONIC PANCREATITIS

One of the main clinical symptoms of CP in humans is pain, occurring either in episodes or as a constant disabling pain[115,116]. Hence, an important goal of treatment for CP is to relieve the pain. The analgesic treatment is often inadequate as the pathophysiology behind CP as well as the mechanisms behind the accompanying pain is not yet fully understood[117]. As described in the previous sections, no single animal model displays all aspects of CP and each of the different models display histological similarities to the human condition to various degrees. In order to improve the pain treatment and obtain more knowledge about the physiology behind CP associated pain, animal models of CP associated pain are needed.

Rat models of CP where pancreatic nociception was investigated, have been established through invasive, non-invasive and spontaneous models[118,119]. In these models pancreatic pain has been shown through both mechanical and thermal stimulation of the abdomen (referred pain[120]) as well as direct electrical stimulation of the pancreas[118,121]. These models had histopathological similarities to the human disease and had progressive fibrosis and inflammation. Furthermore, the models showed correlation between nociceptive behaviour and increased expression of nerve growth factor (NGF) in the pancreas and calcitonin gene-related peptide (CGRP), substance P (SP), proteinase-activated receptor 2 (PAR2), and brain-derived neurotrophic factor (BDNF) in thoracic dorsal root ganglion and spinal cord segments[118,122-124]. Increased expression of NGF, CGRP, SP and BDNF has also been shown in human patients with CP[125-127].

Several animal models have investigated the mechanisms involved in pain accompanying CP. Takamido *et al*[119] reported morphological changes of the nervous system being involved in development of CP pain. This study suggested that elongation of dorsal root ganglia axons and enlargement of intrapancreatic nerve bundles as being a possible mechanism of pain generation in CP. On a supraspinal level, findings have suggested that descending facilitation from the rostral ventromedial medulla plays an important role in persistent pain associated with CP[128]. Furthermore, recent rat experiments have suggested that spinal microglia becomes activated during CP and has an important role in initiating and maintaining chronic pain[129].

TRANSLATION OF PANCREATITIS-ASSOCIATED VISCERAL PAIN STUDY FROM ANIMAL TO HUMAN

It may be difficult to use animal models to study pancreatitis associated visceral pain as pain is a subjective experience. However animal models are needed to explore the molecular mechanisms behind pancreatitis associated visceral pain as this is difficult to study in humans. The molecular mechanisms behind the chronic pain associated with CP are poorly understood, but within recent years, animal experiments have suggested some mechanisms that might be involved. The transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) have been shown to be contributing factors to pain in CP[122,130,131]. It has been shown that CP is accompanied by an increased level of NGF which caused an up-regulation of TRPV1 expression and sensitivity, resulting in hyperalgesia and allodynia[122,130]. TRPA1 is important in both inflammation and pain in CP and can be sensitized through activation of PAR2[131].

The mechanisms mentioned above could be used as targets for the development of novel therapeutics, aiming at treating the chronic pain accompanying CP. Neutralizing antibodies against neurotransmitters such as BDNF and NGF[124,130] or receptor specific antagonists[122] has proven to reverse the characteristic nociceptive behavioral changes induced by CP in several of the experimental models. Furthermore, inhibition of trypsin or inhibition of microglia activation has also abrogated the pain related behavior seen in response to CP[123,129]. All these different mechanisms of pain treatment in CP models could have a potential as targets for novel pharmacological treatment of the chronic pain associated with CP in human patients. Also established analgesic drugs such as gaba-

pentin, buprenorphine, and morphine have been tested in animal models of CP[118,121,132], and shown to have analgesic effect. However, many of these therapeutic approaches need to be tested in humans, before their true potential analgesic treatment of CP pain in humans can be established. It is known that some of these analgesic mechanisms are species specific and specific to the different models of induced CP.

CONCLUSION

Choosing the right model of pancreatitis is difficult and the scientific rationale needs to be carefully considered. Furthermore, no model of pancreatitis parallels all classical symptoms and the question under investigation is of importance when choosing a model. One of the main symptoms of CP is visceral pain and in order to improve the pain treatment and obtain more knowledge about the physiology behind the pancreatitis associated visceral pain, animal models of pancreatitis associated visceral pain are needed.

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