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# The Experimental Models of Acute Pancreatitis

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ABSTRACT

Acute pancreatitis is a severe condition that has a high mortality rate. Animal models of acute pancreatitis have been created to address this issue. Animal models can consistently induce mild, moderate, or severe acute pancreatitis. Caerulein, an analog of cholecystokinin, is administered at supramaximal doses to elicit acute pancreatitis and is one of the most widely used models. In this model, rats develop acute mild edematous pancreatitis, while mice that receive caerulein administration experience acute necrotizing pancreatitis. The most widely used model of acute severe necrotizing pancreatitis in rats is acute pancreatitis induced by the administration of an overdose of caerulein. It is possible to rule out the impact of neurological and hormonal variables on the onset of acute pancreatitis using ex vivo models.

Keywords: Acute mild edematous pancreatitis, acute necrotizing pancreatitis, caerulein, experimental acute pancreatitis.

## INTRODUCTION

### *The hyperstimulation of secretors*

This pancreatitis model is the most commonly used and has been modified extensively. Excessive neurological (cholinergic) stimulation has been known since the late 19th century to cause damage to acinar cells and the production of vacuoles in the pancreas. Rats treated with intravenous cholecystokinin (intestinal hormone) developed a moderate and curable form of pancreatitis, according to research by Lampel and Kern in 1977.[1]

Changes in the intracellular mobility of autophagosomal and secretory enzymes were discovered to have similarities with human disorders while researching secretion-induced pancreatitis. This approach was quickly adopted to investigate prospective treatments. It gained more credence when it was found that supraphysiological stimulation of the pancreas is characterized by the premature and intrapancreatic activation of digesting proteases, such as trypsinogen.[2] When secretogens were used to induce pancreatitis in rats, an intravenous catheter had to be inserted either into the jugular vein or the tail vein. Intraperitoneal injections into mice quickly altered this procedure, enabling the use of transgenic and knockout animals.[1] The most popular method for generating acute pancreatitis in mice is seven intraperitoneal injections of synthetic caerulein at a dose of 50 g/kg body weight, spaced one hour apart. The primary distinction between the murine and rat models is that the former exhibits more significant acinar cell necrosis while the latter exhibits less interstitial edema and intracellular vacuolation.

Furthermore, depending on the model and animal species, autophagy and apoptosis may contribute differently to the development of pancreatitis.[3,4] Using these models, we can research potential treatment modalities and disease mechanisms.[5] These models have become the most widely used model of chronic pancreatitis, even though they require repeated intraperitoneal caerulein injections (over weeks or months). These models are also used to investigate how chronic inflammation contributes to the development of pancreatic cancer.[6,7]

### *The overstimulation of in vitro secretions*

Williams et al. devised a technique for separating functionally intact groups of 3–80 cells, known as pancreatic acini, from rodent pancreas shortly after reporting on the secretogenic pancreatitis model. Later on, this procedure was modified to separate acini from various animals, including people. Collagenase is used to digest the pancreas, and separated acini retain their intracellular signaling and secretory capabilities for up to 4 hours in a buffered environment.[8]

The relationship between pancreatic stimulant secretion and intracellular organelle function was the main focus of early studies on isolated acini. The acinar model was altered once more after it was determined that extra-acinar and non-acinar cell factors also contributed to the development of pancreatitis. Systems for co-incubation and co-culture have been created to enable research on the interactions between acinar cells and inflammatory or stellate cells.[9]

Furthermore, adenoviral gene transfer culture conditions were established to manipulate acinar cells.[10] When introduced to primary cultures, acinar cells progressively lose their capacity to secrete digestive enzymes and dedifferentiate. The physiological tissue context of newly isolated acini produced by collagen digestion has been lost even though they have intact secretory vesicles and secretory stimulation (which includes

activation of intracellular proteases). Their natural tissue context of bile entering the pancreatic duct has yet to be recovered. His two theories were supported by meticulously carried out animal experiments and autopsy results from various patients. Gallstones that obstruct the pancreatic duct prevent pancreatic secretion, which leads to pancreatitis. Bile acid leakage and duct blockage It is well-recognized that gallstone disease is one of the most frequent causes of pancreatitis.[11] Many animal models of pancreatitis have been developed due to experimental research into how gallstones passing through the common bile duct cause pancreatitis. Gallstones can either temporarily block pancreatic secretion or, on the other hand, allow reflux, according to two somewhat contradictory theories put forth by Opie in 1901. If a gallstone becomes lodged in the papilla and connects with the Wirsung duct above the level of blockage, bile can enter the pancreas and cause pancreatitis. However, anatomical research has demonstrated that the model describing the ampullary portion of the common bile duct's structure needs to be corrected. The structure of the biliary-pancreatic duct at the papilla prohibits reflux into the pancreatic duct behind the removed gallstone. There have also been other descriptions of additional factors that reduce the likelihood of the standard channel model.[12-15] Research on the American opossum provides the best evidence against the common channel hypothesis. These investigations demonstrated that the initial events involve acinar cells and that pancreatic outflow obstruction alone is sufficient to cause necrotizing pancreatitis.[14] In models of overstimulated pancreatitis, both positions are critical; however, the roles may be even more crucial in forms of pancreatitis due to ductal obstruction.[16]

*Basic amino acid-induced pancreatitis*

By injecting rats with large doses of l-arginine intraperitoneally, other authors created a non-invasive model of severe pancreatitis with a high death rate.[17] It was then demonstrated that L-arginine could necrotize up to 100% of acinar cells in a concentration-dependent way. The pancreas doubled in weight 24 hours after the first intraperitoneal injection due to edema, primarily caused by endoplasmic reticulum stretching—the acinar cells experienced necrosis after two days. Interstitial tissue made up of fibroblasts and inflammatory cells quickly replaced the necrotic cells.[18] Persistent administration of low arginine dosages may also result in a chronic variation of the illness—the cellular mechanism through which pancreatitis is caused by L-arginine, as opposed to other amino acids. One benefit of the L-arginine model is its severity; in some cases, it can be likened to pancreatitis caused by bile salts. Its drawbacks include unclear pathogenesis and inconsistent results, particularly in mice.

*Food-related pancreatitis*

It was found in the 1930s that the pancreas suffers damage from diets low in choline, an essential nutrient that is part of the vitamin B complex and cell membranes. Severe necrotizing pancreatitis was observed in mice fed a choline-deficient diet enriched with the methionine derivative ethionine (CDE diet). Depending on how many days the mice are fed the CDE diet, they develop hemorrhagic necrosis of the pancreas, and up to 100% of them die within five days. The diet has a similar effect in rats, and although this model was initially developed using young female mice, male mice can be used in this model after estrogen administration.[19] While the pancreatitis caused by the CDE diet is more severe than the pancreatitis caused by necrolysis, both models have similar characteristics, such as the inhibition of digestive enzyme secretion and the creation of cytoplasmic vesicles that contain lysosomal hydrolases colocalized with digestive enzymes. The CDE diet induces pancreatitis by interfering with the stimulus-secretion coupling in acinar cells, which occurs after hormone receptor binding and before apical Ca. Disruption of hormone-stimulated generation is also linked to it. Despite being a non-invasive model, the diet is costly. It demands much work, standardization of procedures on location, and close attention to diet and animal health for every new experiment.

*Immuno-mediated models*

Since the middle of the 20th century, models of acute pancreatitis based on immune mechanisms have been created. Among the first to create this model in 1954 were Thal and Brackney.[20] Their findings showed that hemorrhagic necrotizing pancreatitis was caused by two injections of meningococcal toxin or E. coli into the pancreatic ducts of goats or rabbits within 24 hours. Originally postulated as the local Schwarzmann reaction, the inflammatory mechanism of inflammation was subsequently proposed as the outcome of the Arthus phenomenon. In other investigations, ovalbumin was injected subcutaneously to sensitize the animals, and either ovalbumin or foreign serum was injected into the pancreatic duct to cause pancreatitis. These models were challenging to create technically and could only be used to study specific features of pancreatitis, based primarily on generalized. As a result, their acceptance by researchers was restricted. Afterward, transgenic inbred rodent strain models were created in which immunological defects caused spontaneous pancreatitis. Among the most extensively researched models of spontaneous pancreatitis are MRL/Mp mice, diabetic nonobese mice, and Bonn/Kobori rats.[21-23] Initially, diabetic nonobese mice and Bonn/Kobori rats were used as models for spontaneous pancreatitis development. Prior to the discovery that they also developed chronic pancreatitis, nonobese diabetic mice were recognized as models of spontaneous diabetes.

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Administration of the immunogens such as polycytidylic acid (synthetic, double-stranded polyribonucleotide and immune modulator) or recombinant interferon accelerates the spontaneous development of pancreatitis in MRL/Mp mice. These mice have developed into the most reliable, popular, and clinically applicable models of autoimmune pancreatitis.[24] The disease known as autoimmune pancreatitis is relatively new; its clinical subtypes and histopathological features have only lately been identified.[25-26] As a result, animal models of autoimmune pancreatitis will be employed more often and will be a valuable resource for clarifying the obscure pathophysiology of this illness.[27]

## CONCLUSION

Genetic and environmental factors work together to determine the severity of acute or chronic disease and the chance of developing pancreatitis. For instance, smoking cigarettes appears to raise the risk of both acute and chronic pancreatitis in patients who also consume alcohol. Smoking and alcohol have distinct effects with distinct mechanisms of action. We examined several models that exploit the interactions between various forms of damage to induce illness. When these models have similar or overlapping pathogenic mechanisms, they are accommodating for research. For instance, in rodent models, acute pancreatitis can result from the combination of chronic alcohol consumption and physiological caerulein concentrations but not from either alone.

Similarly, in rats, chronic pancreatitis is only brought on by the combination of alcohol and LPS; neither substance by itself causes the illness. Furthermore, fat also seems to make acute pancreatitis in humans more severe particularly when combined with intrapancreatic fat) and makes rodents more susceptible to diseases caused by cytokines and cerulein. Understanding the pathophysiology of human disease should enable researchers in the future to create pancreatitis models that incorporate pertinent variables and more closely resemble the symptoms seen in patients.

## AUTHOR AFFILIATION

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