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REVIEW

# Do Animal Models of Acute Pancreatitis Reproduce Human Disease?

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**SUMMARY**

Multiple animal models of clinical pancreatitis have been developed, however, limitations with respect to the pathobiology of human disease make it difficult to assess the validity of animal models. Although the growing availability of human pancreatic acinar cells are likely to provide information on early pancreatitis events that can be compared meaningfully with animal models, the relevance of animals to later events may be more difficult to obtain.

**Acute pancreatitis is currently the most common cause of hospital admission among all nonmalignant gastrointestinal diseases. To understand the pathophysiology of the disease and as a potential step toward developing targeted therapies, attempts to induce the disease experimentally began more than 100 years ago. Recent decades have seen progress in developing new experimental pancreatitis models as well as elucidating many underlying cell biological and pathophysiological disease mechanisms. Some models have been developed to reflect specific causes of acute pancreatitis in human beings. However, the paucity of data relating to the molecular mechanisms of human disease, the likelihood that multiple genetic and environmental factors affect the risk of disease development and its severity, and the limited information regarding the natural history of disease in human beings make it difficult to evaluate the value of disease models. Here, we provide an overview of key models and discuss our views on their strengths for characterizing cell biological disease mechanisms or for identifying potential therapeutic targets. We also acknowledge their limitations. *(Cell Mol Gastroenterol Hepatol 2017;4:251–262; http://dx.doi.org/10.1016/j.jcmgh.2017.05.007)***

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Although models of acute pancreatitis have been used for several decades, the extent to which they recapitulate the events in human beings remains unclear. The clinical course and limited pathologic material suggest that features of mild and severe pancreatitis generally are shared between these models and human beings.[1,2] Thus, mild and severe disease, and probably the new intermediate category of moderately severe disease, have similar courses and outcomes, although the time courses may differ, with common rodent models usually progressing more rapidly than human beings.

Some pancreatitis models are designed to examine issues related to the recognized causes of human disease and factors that might modulate disease severity. The major etiologies of acute clinical pancreatitis are gallstones, alcohol, and smoking. Procedure-related, especially after endoscopic retrograde cholangiopancreatography (ERCP), acute pancreatitis (PEP) represents an important subgroup for which specific early interventions appear to reduce disease incidence and severity.[3] Renal failure,[4] diabetes, and especially obesity are substantial risk factors for disease development and severity. Although an infrequent cause of pancreatitis, exposure to potent cholinergic agonists as seen with scorpion bites[5] and exposure to select insecticides[6,7] also can cause disease and may be mimicked by preparations that use supraphysiologic concentrations of toxins or neurohumoral agents to induce disease.[8] Infections with Coxsackie virus can cause acute pancreatitis in children, although the incidence is unclear; this response has been reproduced in animal models.[9] Known genetic factors vary in their clinical impact. For example, mutations in cationic trypsinogen alone can cause pancreatitis, but such mutations make a very small contribution to the clinical load of this disease. Mutations in other molecules such as serine protease inhibitor Kazal-type 1 and cystic fibrosis transmembrane conductance regulator appear to modify the risk of disease in the presence of other accepted factors, such as ethanol abuse. Although genetic models that reflect human variants have been generated, their value in reflecting clinical disease has been limited; we will not comment on these models further in this article.

Investigators striving to mimic these clinical etiologic factors in experimental models have focused on the underlying cellular mechanisms that are operative in these

***Abbreviations used in this paper:*** **CRISPR, clustered regularly interspaced short palindromic repeats; ERCP, endoscopic retrograde cholangiopancreatography; LPS, lipopolysaccharide; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PEP, procedure-related endoscopic retrograde cholangiopancreatography acute pancreatitis; PLA2, phospholipase A2; TRPV1, transient receptor potential vanilloid receptor 1.**

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disease etiologies. In this respect, animal models have been remarkably successful in characterizing intracellular processes that precede tissue injury.[10–12] Whether or not targeting these processes successfully in animal experiments predicts a similar beneficial effect in clinical trials remains another matter (Table 1).

## Animal Models of Clinical Acute Pancreatitis

Studies in experimental acute pancreatitis models are performed with several potential goals in mind. Most often is the wish to reproduce the mechanisms and processes underlying disease and/or examine therapeutic interventions, or use models to examine basic features of acute injury, inflammation, or tissue reconstitution. This means that the timing of an intervention needs to be relevant to the phase of disease. Models also can be used to examine the relationship among organs during the course of acute injury. For example, how does pancreatic injury affect the lungs or the kidneys? Models also can explore factors that directly cause disease, sensitizers that affect the risk of developing disease or modulate its severity, or both. One lesson learned from both studies of models and human pancreatitis is that sequential and overlapping pathologic responses underlie this disease.

Models of acute pancreatitis study the disease at the cellular and whole-animal level and in a range of species. Thus, isolated groups of pancreatic acinar cells long have been used to study basic cell physiology and more recently acute pancreatitis responses. Although they have the advantage of investigating responses in the absence of inflammation and changes in blood flow, their acinar cell phenotype disappears within hours of being placed in culture, making them useful for examining only early pancreatitis responses. Intact animal models of pancreatitis have been generated in many species including dogs, cats, guinea pigs, and even zebra fish.[13,14] Although many species have been used, rats and mice are used most commonly. This is because of their relatively low cost, the high reproducibility of rodent models, our potential to simulate the conditions we believe lead to human disease, and the growing efficiency in manipulating gene structure and function. Here, we focus on rodent models of acute pancreatitis and their potential relevance to human disease beginning with in vivo models and concluding with isolated cell preparations.

**Table 1.** Examples of Factors That Make it Difficult to Assess the Relevance of Acute Pancreatitis Models

| |
|---|
| Rodents |
| Inbred strains and strain differences |
| Variations in microbiome and diet |
| Potential differences in key regulatory/target proteins |
| Differences in preparations/experimental conditions |
| Incomplete information (time course, inflammatory responses, multi-organ effects) |
| Human beings |
| Inherent human genetic and epigenetic variation |
| Lack of knowledge of both how injurious factors cause disease and reproducing them in animal models |
| Paucity of tissue for histologic analysis and correlation |
| Incomplete information relating to the natural history of disease and organ reconstitution |

Although rodent models are used most often, their differences from human exocrine pancreas with regard to various factors, such as digestive enzyme content, should be recognized. Experimental pancreatitis preparations vary in their difficulty, reproducibility, and apparent relevance to clinical disease.[14] Because the clinical relevance of most models remains unclear, some studies have examined the efficacy of interventions using multiple models, which we view as wise.[15,16] Later, we comment on some of the key experimental pancreatitis models.

### Cerulein-Induced Pancreatitis

One of the oldest and most often used models of acute pancreatitis uses cerulein, a peptide orthologue of cholecystokinin, that when given in doses that are 10–100 times greater than a physiologic equivalent, causes mild acute pancreatitis in rats and a somewhat more severe variety in mice.[17,18] From 1 to 12 doses may be given hourly to induce disease. Although this also leads to lung injury, both the pancreatitis and lung injury are fully reversible within hours to a few days of the treatment. Mechanistically, this model is most similar to the pancreatitis caused by scorpion venom and cholinergic toxins that are thought to represent states of supraphysiologic neurohumoral stimulation. The model has been highly favored because of its strong reproducibility, simplicity, and the ease with which processes of intracellular protease activation can be studied.[19,20] It also has been extended to generate other forms of pancreatitis, such as the combination of cerulein with partial duct ligation, which allows simultaneous investigations of acute reversible changes and progressive fibrosis within the same organ.[21] As another example, when cerulein is given in repeated doses over time, the model can be converted to one that generates either severe pancreatitis or one that has features of chronic disease.[22,23] One challenge with the cerulein model is that responses between mice and rats are different. For example, the time course of zymogen activation, the degree of inflammation, and the pattern of cell death are distinct. Furthermore, the ability of repeated doses of cerulein to cause fibrosis in a chronic pancreatitis model depends on the mouse strain.[24] We believe that the cerulein model likely is relevant to initiator mechanisms in acute clinical pancreatitis, at least those that follow the earliest factors such as acinar cell–receptor activation. It also seems probable that prophylactic or therapeutic interventions that fail to show benefit in this model would not reduce injury in more severe models of acute pancreatitis. It is also the model best suited to identify or refute potential treatment targets in a cell biological context because it best preserves acinar cell physiology throughout the experimental disease course.[18,25]

### Alcoholic Pancreatitis

Although a number of models have used different avenues of delivery to generate alcoholic pancreatitis in rodents, the oral route given by diet or gastric infusion (and