International Journal of
Molecular Sciences

MDPI

Review

Murine Models of Acute Pancreatitis: A Critical Appraisal of Clinical Relevance

Pedro Silva-Vaz [1,2,3,*], Ana Margarida Abrantes [4,5,6], Miguel Castelo-Branco [1,3], António Gouveia [2,3], Maria Filomena Botelho [4,5,6] and José Guilherme Tralhão [4,5,6,7]

1 Health Sciences Research Centre, University of Beira Interior (CICS-UBI), 6200-506 Covilhã, Portugal; mcbranco@fcsaude.ubi.pt
2 General Surgery Department, Unidade Local de Saúde de Castelo Branco, 6000-085 Castelo Branco, Portugal; agouveia@ulscb.min-saude.pt
3 Faculty of Health Sciences, University of Beira Interior, 6200-506 Covilhã, Portugal
4 Coimbra Institute for Clinical and Biomedical Research (iCBR) area of Environment Genetics and Oncobiology (CIMAGO), Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal; mabrantes@fmed.uc.pt (A.M.A.); mfbotelho@fmed.uc.pt (M.F.B.); jglrt@hotmail.com (J.G.T.)
5 Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal
6 Biophysics and Biomathematics Institute, IBILI-Faculty of Medicine of University of Coimbra, 3000-548 Coimbra, Portugal
7 Surgery Department, Centro Hospitalar e Universitário de Coimbra, 3000-075 Coimbra, Portugal
* Correspondence: pedro.silvavaz@gmail.com; Tel.: +351-966-498-337

Received: 4 May 2019; Accepted: 5 June 2019; Published: 7 June 2019

Abstract: Acute pancreatitis (AP) is a severe disease associated with high morbidity and mortality. Clinical studies can provide some data concerning the etiology, pathophysiology, and outcomes of this disease. However, the study of early events and new targeted therapies cannot be performed on humans due to ethical reasons. Experimental murine models can be used in the understanding of the pancreatic inflammation, because they are able to closely mimic the main features of human AP, namely their histologic glandular changes and distant organ failure. These models continue to be important research tools for the reproduction of the etiological, environmental, and genetic factors associated with the pathogenesis of this inflammatory pathology and the exploration of novel therapeutic options. This review provides an overview of several murine models of AP. Furthermore, special focus is made on the most frequently carried out models, the protocols used, and their advantages and limitations. Finally, examples are provided of the use of these models to improve knowledge of the mechanisms involved in the pathogenesis, identify new biomarkers of severity, and develop new targeted therapies.

Keywords: acute pancreatitis; animal models; murine; experimental models; biomarkers; inflammation

1. Introduction

Acute pancreatitis (AP), especially severe cases, is a major clinical and financial burden, representing over 320,000 hospital admissions in the United States in 2012 [1]. The incidence of AP ranges from 4.9 to 80 cases per 100,000 persons per year, with equal affinity for each gender [1,2]. The two most common causes of AP are gallstone disease and alcohol [2,3]. The severity and the outcomes are highly variable and unpredictable [4]. Approximately 80% of cases present with mild and interstitial AP. A lower number of patients' courses with a severe form characterized by the presence of persistent organ failure with local and systemic complications associated with a significant morbidity and mortality [5,6]. Mortality in severe form may reach 30% to 50% [1,6,7]. Unfortunately,

the pathophysiology of the AP remains unclear, leading to a lack of effective preventive or therapeutic strategies [8,9].

Evaluating the severity of AP is the major issue that will influence the clinical outcome. Nevertheless, the factors (etiological, environmental, and genetic) that induce severity remain uncertain. The high variability of the severity of AP and the problems in accessing the pancreas in a clinical study have further hindered attempts to clarify its pathophysiology [10]. Therefore, research work using animal models is crucial to increase the understanding of this pathology in order to improve treatments. Since Claude Bernard first debuted the practice in 1856, different animal models have been developed [11], with rodents being the animal most available due to low cost, high reproducibility, mimicking conditions in the human disease [12], and the growing efficiency in manipulating gene structure. An ideal model should be simple and easily reproducible, with the ability to produce controlled severity in order to mimic human disease and answer the experimental question [13]. When performing these models, the researcher should be based on the elevation of pancreatic enzymes, such as amylase and lipase, in order to confirm the induction of AP, taking into account that these enzymes do not reflect the degree of severity. Pancreatitis severity can be assessed by significant histological changes such as interstitial edema, acinar cell death, parenchymal loss, hemorrhage, inflammatory cell infiltration, and vacuolization, and the evaluation of local or systemic complications, with the lung being the organ most involved [14].

In this review, an overview of murine models of AP will be discussed, with special focus on protocols used and their advantages and limitations. Furthermore, examples of the use of these models with the objective of improving the knowledge of the mechanisms involved in the pathogenesis, identifying new biomarkers of severity, and developing new targeted therapies are also provided.

2. Applicability of Murine Models to Assess the Severity of Acute Pancreatitis

Banks et al. [6] defined and stratified the severity of AP into three degrees: mild, moderately severe, and severe, based on the absence or presence of persistent organ failure and local or systemic complications. As the severe form is associated with extensive disease characterized by significant pancreatic necrosis and systemic inflammation, which may lead to multiorgan failure and death, the early prediction of severity becomes a major issue in the management of AP.

The severity of AP in murine models is difficult to predict. Nevertheless, some models are associated with mild AP, while others are associated with severe AP (Table 1). The severity of AP is assessed by inflammatory markers and histologic changes. The inflammatory markers most commonly used are protein C-reactive [15], pro-inflammatory cytokines [16,17], tumor necrosis factor-α [18], and procalcitonin [19]. Concerning histological evaluation, Schmidt et al. [20] published the first and most commonly cited scoring system. It uses five parameters: edema, acinar necrosis, hemorrhage and fat necrosis, and inflammation and perivascular infiltrate. Besides pancreatic evaluation (edema, inflammatory infiltration, parenchymal necrosis and hemorrhage), Ding et al. [21] also assessed the liver, kidney, and lung for histological changes. Klopfleisch [22], in his systematic review, analyzed the available histologic scores, concluding that all are based on the Schmidt score having been modified marginally with the omission of a single parameter or including vacuolization as an additional parameter.

However, a severity score related to the Revised Atlanta Classification [6] is not available, to our knowledge, which stratifies murine models of AP in mild, moderately severe, and severe. This tool would be very important to increase the clinical relevance of murine models of AP.

Table 1. Animal models for acute pancreatitis according to the severity degree.

AP Classification (According Revised Atlanta Classification [6])	Animals	Models
Mild acute pancreatitis - No organ failure - No local or systemic complications	Rats	Hormone-induced model
Moderately severe acute pancreatitis - Organ failure that resolves within 48 h - Local or systemic complications without persistent organ failure		-
Severe acute pancreatitis - Persistent organ failure (>48 h) - Single organ failure - Multiple organ failure	Mice	Hormone-induced model
	Mice and Rats	Closed duodenal loop model *
	Mice	Alcohol-induced model *
	Mice and Rats	Nutrient-induced model
	Mice and Rats	Biliopancreatic duct injection model
	Mice and Rats	Vascular-induced model
	Mice and Rats	Ischemia/Reperfusion model *
	Mice and Rats	Duct ligation model *

The severity of AP is a very important issue for the correct approach of this disease. The choice of the model and animal is crucial for the correct design and answer to the question under study. * In several studies, the AP severity is very variable.

3. Murine Models and the Etiology of Acute Pancreatitis

Gallstones remain the most common cause of AP, while up to 25% to 30% of cases can be attributed to alcohol [7]. Despite these two more frequent etiologies, other factors, in 10% of the cases that are described, can influence the severity, such as endoscopic retrograde cholangiopancreatography [23], renal failure [24], diabetes [25], obesity [26], tobacco [27], drugs and toxins [28], genetic factors [29], trauma [30], autoimmune [31], and hyperlipidemia [32].

Since the pathophysiology of this disease is not well understood, it is fundamental to study each cause of AP in order to understand the underlying mechanisms. In this sense, researchers make a great effort to mimic these clinical etiologic factors in murine models. Studies suggest that murine models have successfully characterized intracellular processes that precede tissue injury.

Due to this, it is important that the researcher has knowledge about each murine model and the clinical etiologic factor that mimics AP to better evaluate the issue that is being addressed (Table 2).

Table 2. Animal models for acute pancreatitis according to the etiology and factors.

	Animals	Models
Etiology	Mice and rats	*Biliary pancreatitis* Biliopancreatic duct injection model Duct ligation model *Alcoholic pancreatitis* Alcohol-induced model
Factors	Mice and rats	*Bacterial translocation* Closed duodenal loop model Duct ligation model *Microcirculation impairment* Vascular-induced model Ischemia/Reperfusion model *Cholinergic agents* Hormone-induced model *Diets* Nutrient-induced model *Genetic* Gene knockout model *Trauma* Ischemia/Reperfusion model Closed duodenal loop model

Murine models are most commonly used to study AP. In mice and rats, AP (acute inflammation with necrosis and hemorrhage when severe) can be induced by injections of caerulein, alcohol, bile salt infusion, duct ligation, several nutrients such as choline-deficient ethionine-supplemented diet and L-arginine, closed duodenal loop, alterations in genetic animal structure, and changes of pancreatic vascular irrigation. Whether these models produce all the characteristics of human AP remains unclear.

4. Murine Models: A Practical Overview

4.1. Hormone-Induced or Hyperstimulation Acute Pancreatitis Model

Normal pancreatic metabolism is associated with physiological concentrations of secretagogues. AP results from an excess availability of secretagogues, which leads to a high secretion of pancreatic digestive enzymes. One of the most frequently used is caerulein, which is a decapeptide cholecystokinin analogue that stimulates pancreatic secretion. This model histologically simulates the early phase of AP in humans [33]. Mild, interstitial, and edematous pancreatitis was developed by Lampel et al. [34] in rats and severe AP with necrosis of acinar cells was developed by Niederau et al. [35] in mice. The continuous infusion of supramaximal caerulein can be administrated intravenously [34,36,37], subcutaneously [38,39], or intraperitoneally [40], with intravenous being the best way of administering the hormone to rats and mice. However, it is not commonly performed due to the requirement of vascular cannulation and anesthesia. This method was modified via intraperitoneal in the lower left or right quadrant of the abdomen. Between one and 12 doses may be given hourly, via subcutaneous or intraperitoneal, to induce AP. Table 3 summarizes the different routes of administration of caerulein, as well as the most commonly used doses. Histologically interstitial edema develops one hour after the infusion, with a maximum after 12 h [34]. This model has been useful for the evaluation of the AP by analyzing the pathophysiology [41–44], severity [45–49], target therapies [50–54], course, outcomes [55], and related pulmonary [56,57] and cardiac [58] injuries. It also mimics the pathophysiology of AP caused by scorpion venom [59] and cholinergic toxins [60] in humans. The exact mechanism by which caerulein induces disease is not totally understood. Studies have shown that caerulein causes an abnormal localization of the zymogen and lysosomal hydrolases that are activated intracellularly within the acinar cells [61]. In its turn, lysosomal cysteine protease cathepsin B appears to be an important factor in the activation of trypsinogen to trypsin [62]. This model has also been used in the study of the identification of new protein alterations and biomarkers [63] characterizing pancreatic inflammatory damage with proteomic [64] and metabolomic [65] analysis. The advantages of this model are its

noninvasiveness, inexpensiveness, rapid induction, and wide reproducibility and applicability. It could also be applied to in vitro research [66], and also be used for evaluating systemic disease progression, since it is an important tool for researching the pulmonary involvement of AP [67,68]. The major disadvantage is that only a mild form is developed, and the clinical relevance is limited.

Table 3. Protocols of the most used acute pancreatitis (AP) models in mice and rats. BW: body weight.

AP Model	Animals	Protocols		References	Clinical Relevance
		Administration Route	**Doses**		
caerulein	**mice**	**Intravenous**	6 h continuous infusion of 100 µg/kg/h	[37]	- Relevant to understanding the early AP mechanisms - Pulmonary injury mimics the respiratory involvement in humans - Structural changes of acinar cells are similar to human AP - Preserves acinar physiology throughout the experimental disease course - Mimics the pathophysiology of AP caused by scorpion venom and cholinergic toxins in humans
		subcutaneous	7 h of injections at 50 µg/kg	[39]	
		intraperitoneal	8 h of injections of 10 µg/mL, 0.2 mL/mouse) over two consecutive days	[40]	
			7 h of injections at 50 µg/kg	[44,45]	
			50 µg/kg every two hours for five rounds	[42]	
			10 h of injections at 50 µg/kg	[41,43]	
	rats	intravenous	5 µg/kg/h for periods up to 24 h	[34]	
			3–h continuous infusion of 7.5 µg/kg/h (7.5 µg/kg/h × 3 h)	[36]	
		subcutaneous	5 µg/kg/h for 3 h (hourly injection)	[38]	
			Four injections of 20 µg/kg/h hourly	[47,51]	
			Injection of 10 µg/kg	[50]	
		intraperitoneal	Two injections of 40 µg/kg at hourly intervals	[46]	
alcohol	mice	oral or intragastric	Single intragastric dose of ethanol (6.0 g/kg BW) in NRF2-KO mice	[69]	- Poor clinical relevance
		intraperitoneal	Two intraperitoneal injections of ethanol (1.32 g/kg BW) and palmitoleic acid (1.5 mg/kg BW), separated by one hour	[70]	
	rats	intravenous	Bolus of 2 g/kg BW followed by continuous IV alcohol application of 0.365 g/kg BW/h with an additional 3 mL/kg BW saline solution	[71]	
		oral or intragastric	Intragastric bolus of ethanol 2.3 g/kg BW followed by the continuous infusion of 0.365 g/kg BW/h IV	[71]	
		intraductal	Injection of 48% ethyl alcohol in a volume of 1 cm^3 into the common biliary duct	[72]	
L-arginine	rats	intraperitoneal	2-h injections of 8%	[73]	- Mimics the circulatory, respiratory, and renal alterations that occur in human AP
			250–500 mg/100 g BW	[74]	
Duct infusion-induced model	mice	sodium taurocholate	10 µL/min for 5 min of 2.5–5%	[75]	- Clinical relevance is unclear
	rats	sodium taurocholate	5–10 mM with caerulein intravenous 5 µg/kg/h for 6 h	[76,77]	
			1 mL/kg of 3% injected over a 60-second period	[78–80]	

The most used protocols in AP animal models are described in the sense of helping those who intend to work in murine models. The potential of combining the existing models in the genetically modified murine animals will improve the knowledge of the pathophysiology process underlying AP.

4.2. Alcohol-Induced Acute Pancreatitis Model

One of the major etiologic factors of AP is alcohol. However, it is well documented that AP induced by alcohol alone has been difficult to achieve [81,82]. Foitzik et al. [83] developed a study to evaluate the factors thought to be involved in the pathogenesis of AP associated with alcohol, since alcohol causes pancreatic injury only when combined with other factors such as exocrine hyperstimulation. The most commonly used are secretagogues [82], lipopolysaccharides [84], or palmitoleic acid [70,85]. This model has been used to analyze the effects of alcohol on pancreatic microcirculation, regeneration, and the role of oxidative stress [86]. The alcohol-induced model could be performed via intravenous [71], oral [69,71], intraperitoneal [70], and intraductal [72] administration. Table 3 summarizes the different routes of administration of alcohol, as well as the most commonly used doses. Huang et al. [70] studied the relative importance of oxidative and non-oxidative pathways in mitochondrial dysfunction, pancreatic damage, and the development of alcoholic AP, and whether the deleterious effects of non-oxidative metabolism of alcohol are preventable. This study enabled researching potential specific

treatments via the inhibition of the generation of fatty acid ethyl esters. Kiziler at al. [72] measured markers of oxidative damage in pancreatic tissue, studying how alcohol injures pancreatic parenchyma tissue. They induced AP by the injection of ethyl alcohol into the common biliopancreatic duct. The authors concluded that iron in serum and pancreatic tissue in rats with early-stage AP was associated with several microvascular changes and oxidative pancreatic injury. Schneider et al. [71] showed that the intravenous alcohol-induced pancreatitis offers a valid model. Studies have suggested that alcohol is related with an increase in ischemia damage and have shown the direct damage of the pancreas [87]. This model is relatively simple and can be performed at a low cost. The major disadvantage is the difficulty in reproducing it and its low clinical relevance. The failure to reproduce acute pancreatitis reflects the human condition, and it is necessary to take into account an additional sensitizing factor or a genetic predisposition regarding the development of alcoholic AP.

4.3. Gene Knockout Acute Pancreatitis Model

The gene knockout models played a key role in understanding the relevance of genetic factors in AP. A knockout mouse model provides a more efficient way to study the impact of complete loss of function or the deletion of a gene during disease initiation and progression. The process of targeting gene provides the ability to alter a specific gene in order to better discern its biological role [88]. Mice are currently the most closely related animal to humans, because both species share about 99% of the same genes [89], for which this technique can easily be applied. This animal has the ability to obtain real totipotent embryonic stem cells [90]. Gene knockout in rats is much harder, and has only been possible since 2003 [91]. These models are usually used to evaluate the pathogenesis and outcomes of AP [69]. Venglovecz et al. [43] using aquaporin 1 knockout mice, concluded that aquaporin 1 plays an essential role in pancreatic ductal fluid and bicarbonate secretion, which probably contributes to the increased susceptibility of pancreatic inflammation. Tao et al. [92] studied the role of β-arrestins, which are the regulators and mediators of a G protein-coupled receptor signaling, in pancreatic inflammation. They observed that β-arrestin 1 alleviates AP, and it may be used as a potential therapeutic target. Norkina et al. [93] studied the involvement of the Reg/PAP cell stress gene in the protection or recovery from pancreatic injury. They concluded that Reg/PAP cell stress genes may be protective due to their anti-apoptotic activity. Jancsó et al. [94] used CTRB1-deficient mice to study the role of chymotrypsin in the early phase of AP. They concluded that CTRB1 protects against secretagogue-induced pancreatitis by reducing trypsin activity. This study highlights the role of protease inhibitors in target therapies of AP. The gene knockout models are also an important tool to study the pancreatic inflammation changes and characterized multiorgan failure [95,96]. The gene knockout model is expensive and complex; its major advantage is that by deleting the specific gene under study, its specific function or effect could be analyzed more efficiently.

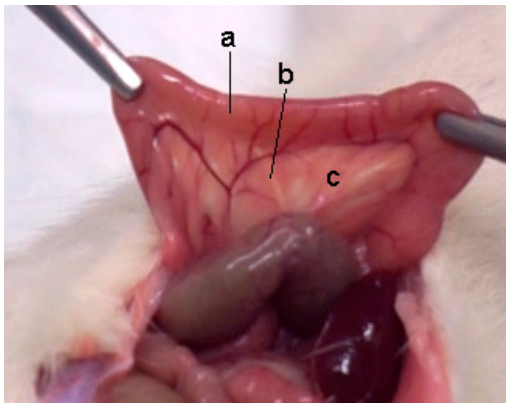
4.4. Nutrient-Induced Acute Pancreatitis Model

AP induced in rats treated with ethionine was described by Faber and Popper [97]. This model has frequently been used to study the pathogenesis of AP and histologic changes of pancreatic parenchymal cells. Lombardi et al. [98] observed hemorrhagic AP with massive fat necrosis in the peritoneal cavity with a total mortality of mice after a choline-deficient ethionine diet. Although the molecular mechanism remains unclear, a choline-deficient ethionine diet and arginine or other basic amino acids cause severe AP associated with a high mortality [99]. They also showed that a choline-deficient diet without ethionine did not cause pancreatic inflammation or mortality [98]. Guilliland and Steer [100] changed the original model, allowing the gradation of AP severity and mortality in order to further study the outcomes of this disease. The choline-deficient ethionine diet model is widely used since it is a noninvasive model, avoiding exogeneous shock. This model was used to evaluate the involvement of pancreatic stellate cells in the development of fibrosis associated to AP [101], and has been used recently to evaluate the signaling pathway that promotes inflammation [96] and new target therapies [102]. The induction of AP can also be achieved with arginine. Mizunuma et al. [103] proposed a model that

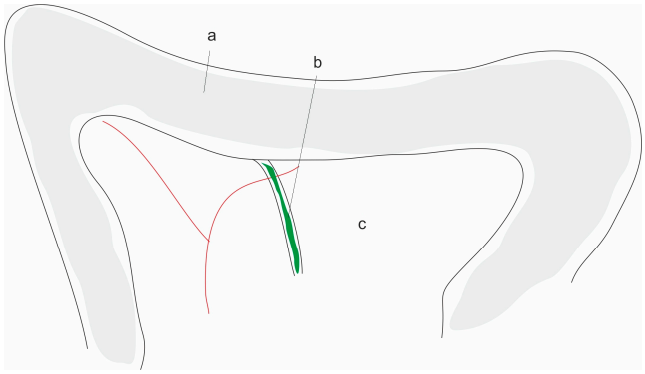
established the intraperitoneal route with L-arginine hydrochloride. Several modifications of this model showed that higher doses can produce high mortality, repeated doses promote necrosis, and reduced doses may delay the time of onset of AP [73,74,104]. Table 3 summarizes the most commonly used doses of L-arginine when administered by the intraperitoneal route. A histological examination revealed degenerative changes to intracellular organelles and the nuclei of acinar cells [105]. Uçmak et al. [106] induced AP with an L-arginine model to investigate the potential effect of silybin, which is a potent antioxidant. They verified that silybin, when used in a prophylactic rather, ameliorates serum oxidative stress parameters. The advantage of this model is its high reproducibility and applicability for researching the different phases of AP and evaluating distant organ injury. The major disadvantage of the arginine-induced AP model is its low clinical relevance, since only two clinical cases of arginine AP in humans are described [107,108].

4.5. Closed Duodenal Loop Acute Pancreatitis Model

In a normal physiological environment, verifying a pressure gradient between the common bile duct and duodenum prevents the duodenopancreatic reflux. The closed duodenal loop model, by changing this normal condition, increases intraduodenal luminal pressure, causing reflux and leading to AP. This model is characterized by the ligation of the duodenum proximal and distal to the union of the common biliopancreatic duct (Figure 1A,B and Figure 2) [109]. The histopathological changes verified with this model consist of intralobular edema, and progressively hemorrhagic pancreatic necrosis [110]. This model is more suitable for the study of pancreatic necrosis as well as for the study of new therapies [110]. Adler, Kern, and Scheele [111] proposed the cannulation of the bile duct to divert the bile away from the duodenum and avoid the involvement of bile in the ensuing pancreatitis, and bile is normally diverted into the jejunum. Several researchers modified this model [112], producing necrohemorrhagic AP. These findings support that the reflux of the duodenal contents into the pancreatic duct is an important mechanism in the development of AP. Other authors [113] instill infected bile or bile sterilized into the duodenum under pressure, producing severe AP. Since this model is associated with a high mortality of the rats, some researchers modified the original model to a temporary ligation of the duodenum [114]. This model is also suitable for the study of bacterial translocation during AP, since the discontinuation of the duodenum leads to functional changes in the mucosal barrier, causing small bowel bacterial overgrowth [115,116]. Sugimoto et al. [117] developed a model of reversible pancreatitis, with an incomplete closed duodenal loop model. They demonstrated that the damage of microcirculation due to tissue ischemia played a role in the increasing severity of AP. This model clarified the role of microcirculation impairment in the pathogenesis of AP, allowing for the research of targeted therapies. The advantage is its simplicity, reproducibility, and use on small animals such as rats. However, the need for surgical intervention, the increased pressure levels verified in the closed duodenal compartment, and the pancreatic duct, as well as the controversial role of bacterial infection, make this model not widely used in scientific research. However, this model has clinical relevance, since there are cases of AP associated with duodenal obstruction in medical literature [118].



A



B

Figure 1. (**A**) Rat pancreas anatomy. Image: The pancreas of an adult rat showing the duodenum and common biliopancreatic duct. Rodent pancreas is soft and diffuse compared with the human pancreas. Photo provided by authors lab. a- duodenum; b- common biliopancreatic duct; c- pancreas. (**B**) Schematic showing the anatomy of rat pancreas. Image: picture showing the schematic anatomy of the pancreas, duodenum, and common biliopancreatic duct. a- duodenum; b- common biliopancreatic duct; c- pancreas.

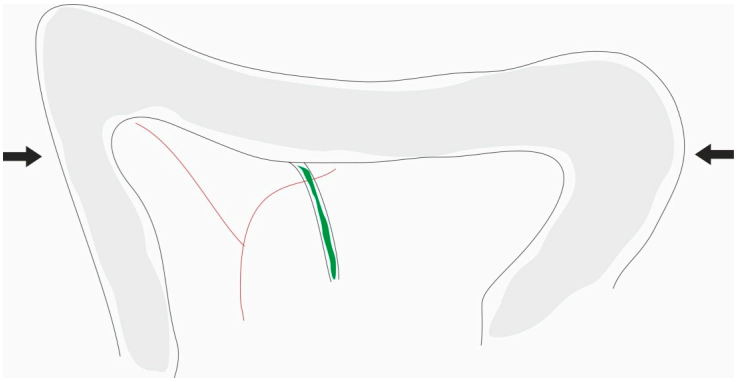


Figure 2. Closed duodenal loop acute pancreatitis model. Image: picture showing the location of the closed loop of the duodenum. According to aseptic techniques, the duodenum is exposed by a laparotomy, the common biliopancreatic duct is identified, and the duodenum is obstructed by the placement of two ligatures: one just beyond the pylorus—that is, proximally to the duct—and the second placed distally to the duct (arrows).

4.6. Biliopancreatic Duct Injection Acute Pancreatitis Model

The dissection of the pancreatic duct and its cannulation provides an alternative way of inducing an experimental AP model. The original model was developed in cats, in 1979, by Reber et al. [119]. Several modifications were made in order to reduce the degree of technical difficulty. The most common surgical technique (Figure 3) consists of a duodenotomy, which is a retrograde injection of bile salts (with or without activated pancreatic enzymes) into the pancreatic duct at the ampulla that leads to severe AP [120]. To induce AP, some compounds infused into the pancreatic duct are used, such as sodium glycodeoxycholic [20] and sodium taurocholate [78,79,121–123] being the last the most used, because it is thought to be the one that most resembles clinical biliary pancreatitis [124]. This bile salt can also be used to induce biliary AP with multiple organ failure. The severity of AP can be obtained by changing either the pressure or the concentration of the bile salt that is used. The severe form is characterized by edema, necrosis, and hemorrhage. The infusion of solution sodium taurocholate induced acute hemorrhagic pancreatitis with mortality range between 24–100% [75–77,80,125,126]. Table 3 summarizes the different doses of sodium taurocholate that are most commonly used. This model is appropriate to study both local and systemic complications of AP, and it can be used to study target therapies. To improve its limitations, this model was changed by combining low-dose intraductal glycodeoxycholic acid with intravenous caerulein [20]. The severity achieved with this model is similar to human disease, and for this reason, it could be used for the study of AP pathogenesis [127,128] and target therapies [129]. This is an easy and reproducible model for severe AP. However, an important limitation is its clinical and pathogenic relevance due to the questionable role of duodenal reflux in the pathogenesis of AP. Another disadvantage is the impossibility of quantifying the pressure with which the solution is applied to cause AP.

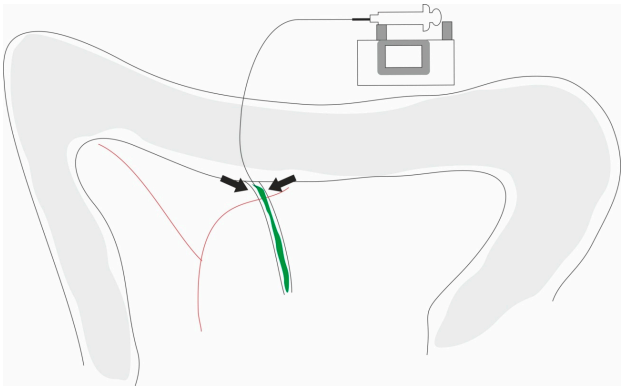


Figure 3. Biliopancreatic duct injection acute pancreatitis model. Image: picture showing the retrograde ductal infusion technique. According to aseptic techniques, the duodenum is exposed by a laparotomy, and the common biliopancreatic duct is identified and cannulated; after the retrograde infusion, the duct is ligated (arrows).

4.7. Vascular-Induced Acute Pancreatitis Model

Pancreatic microcirculatory failure is the major cause of mortality in severe AP, and is thought to be crucial in the early events of AP with multiple organ dysfunction syndrome [130]. The decrease of pancreatic microcirculatory blood flow volume and velocity, and the increase of microvascular permeability lead to pancreas edema and inflammatory infiltration in the early phase of AP [131]. In 1962, Pfeffer et al. [132] found that different degrees of occlusion of the pancreatic microcirculation cause different pancreatic changes, from edema to acute hemorrhagic, necrotizing pancreatitis. This is particularly useful in the study of coagulopathy and the thrombosis of microvessels [133]. Liu et al. [134] studied the effect of vascular bradykinin on pancreatic microcirculation in rats with severe AP. They concluded that vascular bradykinin can improve pancreatic microcirculation. In addition, several studies have been performed to occlude pancreatic arteries [135] and veins [136]. The advantage of

the vascular model is that it is relatively inexpensive, although it does not reliably induce the same degree of severity of AP. However, it is important for studying microcirculatory disorders such as coagulopathy or microvascular thrombosis. The disadvantages are the dramatic surgical trauma exerted upon the animals, the need for a tight protocol, and specific surgical resources.

4.8. Ischemia/Reperfusion Acute Pancreatitis Model

The role of ischemic injury as a cause of AP is well known. Some studies have shown a correlation between the impairment of pancreatic microcirculation and the degree of ischemic injury. Pancreatic microcirculation is the target of reperfusion injury after ischemic. Hoffman et al. [137] developed a model of complete ischemic/reperfusion of the pancreas in rat, causing pancreatic microvascular failure. The severity of changes depends on the duration of ischemia and reperfusion. Dembinski et al. [138] induced AP by clamping the inferior splenic artery for 30 minutes. They induced necrotizing AP with subsequent regeneration within a few weeks. The ischemic/reperfusion model has been used for the study of target therapies such as obestatin [139] and ghrelin [140] and for the study of several biomarkers [141]. The major disadvantages of this model include its reproducibility, being incomplete ischemia, and the inability to measure the remaining pancreatic blood supply. The irreversible ischemia makes this model unsuitable for reperfusion studies. Furthermore, it is difficult to achieve the quantitative analysis of the post-ischemic reperfusion failure.

4.9. Duct Ligation Acute Pancreatitis Model

AP may be induced by ligating the distal bile duct at the level of the duodenum (Figure 4). The first report that associated this model to changes in the exocrine function of the pancreas refers to Churg et al. [142]. This model was used by several researchers to study the pathogenesis [143] and target therapies [144,145], and was developed in an attempt to mimic the clinical situation of a gallstone that obstructed the ampullary orifice with the consequent reflux of bile into the pancreatic duct that lead to AP. In rats, the initial changes such as edema, inflammation, and hyperamylasemia are compatible with AP [146]. This model also induces obstructive hepatic cholestasis and hepatic cholangitis in rats. However, in order to improve this model, some changes were made, namely the combination of pancreatic duct ligation and secretory stimulation, such as caerulein or sodium taurocholate. Studies have shown that in the duct ligation model in rats, the predominant mechanism of cell death is apoptosis. This model may be suitable for the study of bacterial translocation, since the obstruction of bile flow into the intestine causes small bowel bacterial overgrowth [116]. The exclusion of the pancreatic proteases in the gut lumen also alters the intestinal permeability [147]. The advantage of the duct ligation model is that it avoids artificial drug usage, which may produce unwanted systemic effects, as well as the theory relating to clinical biliary AP with biliary pancreatic reflux. However, this is a complex and technically difficult model, and has an associated high cost.

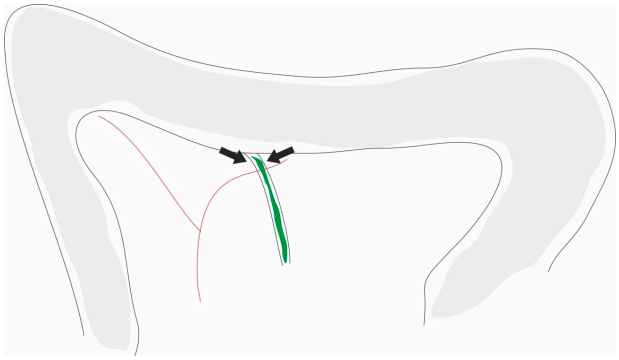


Figure 4. Image: picture showing the site of ligation of the common biliopancreatic duct in the rat. According to aseptic techniques, the duodenum is exposed by a laparotomy; the common biliopancreatic duct is identified and ligated at the level of the duodenum (arrows).

5. Clinical Relevance of the Models and Future Directions

Personalized medicine has become a major research topic in the scientific community. This approach will, in the patient's prolonged life, improve their quality in the future, bringing new challenges to health care. This prolonged lifetime will increase the incidence of AP as well as more severe forms associated with the patient's clinical condition and its comorbidities. This scenario makes the deepening knowledge of the pathophysiology of AP extremely important. Although the clinical relevance of murine models of AP is a controversial subject, they have contributed greatly to the elucidation of the pathophysiology of this important disease.

The clinical presentation of AP is very variable, from mild to moderately severe and severe, with the latter characterized by the persistence of multiorgan failure [6]. Severe AP associated with infected necrosis represents a very high morbidity and mortality. The actual management of severe AP is based on intravenous fluid therapy [148,149], pain control [150], and adequate nutrition [151], utilizing all of these is the best way to prevent early deaths. In cases of infected necrotizing pancreatitis, an endoscopic or surgical step-up approach is evaluated according to each patient and clinical condition [152]. The complexity of AP in human patients is very high, making it difficult for any of the murine animal models available to develop the disease with all the features comparable to human disease. This is true: since predicting the AP severity of each model is difficult, most studies do not stratify animals into moderately severe forms, and there is no severity histologic score that stratifies animals into the three degrees of AP severity. This issue is of extreme importance, since it will allow a more adequate translation of outcomes, and will influence the methodology adopted in each study in the context of the question being addressed.

However, murine models will continue to be an indispensable tool for the study of AP; they will also improve the outcomes of this condition in humans, not only in the field of prevention, but also in attempting new targeted therapies. Unfortunately, most of the results achieved in these models are not confirmed when translated to human studies.

The choice of the best model is fundamental, and should be based either on the etiology or on the risk factors that might modulate disease severity, always keeping in mind the goal of the research.

6. Conclusions

In order to circumvent the limitations and maximize the advantages of each murine model, improvements and combinations of the models have been made to reproduce the disease in humans. These models should attempt to replicate the mechanisms and processes underlying the disease, examine therapeutic interventions, and analyze basic characteristics of acute injury, inflammation, or tissue reconstitution. However, at the present time, none of the existing murine models of AP are totally acceptable. Murine models have considerably contributed to the understanding of the pathophysiologic mechanisms of AP. Therefore, further elaboration of protocols is needed to improve and facilitate the choice of a specific model for a specific question. In this sense, it is essential to invest in the translational research, since these models are an important tool for improving medical care and outcomes for patients with AP.

Author Contributions: P.S.V. and A.M.A. read articles of murine animal models of acute pancreatitis. P.S.V. wrote the review. P.S.V., A.M.A., M.C.-B., A.G., M.F.B., J.G.T. read and approved the final manuscript.

Acknowledgments: P.S.V. is grateful to the members of my research group for their discussion and suggestions during the course of this review. This research was funded by FCT, Portugal (Strategic Project PEst-C/SAU/UI3282/2013 e UID/NEU/04539/2013), COMPETE-FEDER.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Garg, S.K.; Sarvepalli, S.; Campbell, J.P.; Obaitan, I.; Singh, D.; Bazerbachi, F.; Singh, R.; Sanaka, M.R. Incidence, Admission Rates, and Predictors, and Economic Burden of Adult Emergency Visits for Acute Pancreatitis. *J. Clin. Gastroenterol.* **2019**, *53*, 220–225. [CrossRef] [PubMed]
2. Garber, A.; Frakes, C.; Arora, Z.; Chahal, P. Mechanisms and Management of Acute Pancreatitis. *Gastroenterol. Res. Pract.* **2018**, *2018*, 6218798. [CrossRef] [PubMed]
3. Jha, R.K.; Ma, Q.; Sha, H.; Palikhe, M. Acute pancreatitis: A literature review. *Med Sci. Monit.* **2009**, *15*, RA147–RA156. [PubMed]
4. Ikeura, T.; Horibe, M.; Sanui, M.; Sasaki, M.; Kuwagata, Y.; Nishi, K.; Kariya, S.; Sawano, H.; Goto, T.; Hamada, T. Validation of the efficacy of the prognostic factor score in the Japanese severity criteria for severe acute pancreatitis: A large multicenter study. *United Eur. Gastroenterol. J.* **2017**, *5*, 389–397. [CrossRef] [PubMed]
5. Frossard, J.L.; Steer, M.L.; Pastor, C.M. Acute pancreatitis. *Lancet* **2008**, *371*, 143–152. [CrossRef]
6. Banks, P.A.; Bollen, T.L.; Dervenis, C.; Gooszen, H.G.; Johnson, C.D.; Sarr, M.G.; Tsiotos, G.G.; Vege, S.S.; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. *Gut* **2013**, *62*, 102–111. [CrossRef] [PubMed]
7. Shah, A.P.; Mourad, M.M.; Bramhall, S.R. Acute pancreatitis: Current perspectives on diagnosis and management. *J. Inflamm. Res.* **2018**, *11*, 77. [CrossRef] [PubMed]
8. Kambhampati, S.; Park, W.; Habtezion, A. Pharmacologic therapy for acute pancreatitis. *World J. Gastroenterol.* **2014**, *20*, 16868. [CrossRef]
9. Gukovskaya, A.S.; Pandol, S.J.; Gukovsky, I. New insights into the pathways initiating and driving pancreatitis. *Curr. Opin. Gastroenterol.* **2016**, *32*, 429–435. [CrossRef]
10. Steer, M.L. Search for the trigger mechanism of pancreatitis. *Gastroenterology* **1984**, *86*, 764–766.
11. Bernard, C. *Lecons de Physiologie Experimentale Appliquee a la Medecine, Faites au College de France par M. Claude Bernard: Cours du Semestre d'ete 1855*; Bailliere: Paris, France, 1856; Volume 2.
12. Gorelick, F.S.; Lerch, M.M. Do animal models of acute pancreatitis reproduce human disease? *Cell. Mol. Gastroenterol. Hepatol.* **2017**, *4*, 251–262. [CrossRef] [PubMed]
13. Su, K.H.; Cuthbertson, C.; Christophi, C. Review of experimental animal models of acute pancreatitis. *HPB* **2006**, *8*, 264–286. [CrossRef] [PubMed]
14. Samanta, J.; Singh, S.; Arora, S.; Muktesh, G.; Aggarwal, A.; Dhaka, N.; Sinha, S.K.; Gupta, V.; Sharma, V.; Kochhar, R. Cytokine profile in prediction of acute lung injury in patients with acute pancreatitis. *Pancreatology* **2018**, *18*, 878–884. [CrossRef] [PubMed]
15. Chen, K.-L.; Lv, Z.-Y.; Yang, H.-W.; Liu, Y.; Long, F.-W.; Zhou, B.; Sun, X.-F.; Peng, Z.-H.; Zhou, Z.-G.; Li, Y. Effects of tocilizumab on experimental severe acute pancreatitis and associated acute lung injury. *Crit. Care Med.* **2016**, *44*, e664–e677. [CrossRef] [PubMed]
16. Wu, J.; Ma, X.; Chen, W.; Yang, N.; Gao, L.; Mao, W.; Yang, J.; Yang, Q.; Dong, J.; Tong, Z. Protective effects of HTD4010, a Reg3α/PAP-derived peptide, in mouse model of acute pancreatitis via toll-like receptor 4 pathway. *Biochem. Biophys. Res. Commun.* **2019**, *512*, 670–677. [CrossRef] [PubMed]
17. Khurana, A.; Sikha, M.S.; Ramesh, K.; Venkatesh, P.; Godugu, C. Modulation of cerulein-induced pancreatic inflammation by hydroalcoholic extract of curry leaf (*Murraya koenigii*). *Phytother. Res.* **2019**, *33*, 1510–1525. [CrossRef]
18. Yu, W.-Q.; Zhang, S.-Y.; Fu, S.-Q.; Fu, Q.-H.; Lu, W.-N.; Zhang, J.; Liang, Z.-Y.; Zhang, Y.; Liang, T.-B. Dexamethasone protects the glycocalyx on the kidney microvascular endothelium during severe acute pancreatitis. *J. Zhejiang Univ. Sci. B* **2019**, *20*, 355–362. [CrossRef]
19. Soyalp, M.; Yalcin, M.; Oter, V.; Ozgonul, A. Investigation of procalcitonin, IL-6, oxidative stress index (OSI) plasma and tissue levels in experimental mild and severe pancreatitis in rats. *Bratisl. Lek. Listy* **2017**, *118*, 137–141. [CrossRef] [PubMed]
20. Schmidt, J.; Rattner, D.W.; Lewandrowski, K.; Compton, C.C.; Mandavilli, U.; Knoefel, W.T.; Warshaw, A.L. A better model of acute pancreatitis for evaluating therapy. *Ann. Surg.* **1992**, *215*, 44–56. [CrossRef]
21. Ding, S.-P.; Li, J.-C.; Jin, C. A mouse model of severe acute pancreatitis induced with caerulein and lipopolysaccharide. *World J. Gastroenterol.* **2003**, *9*, 584–589. [CrossRef]

22. Klopfleisch, R. Multiparametric and semiquantitative scoring systems for the evaluation of mouse model histopathology-a systematic review. *BMC Vet. Res.* **2013**, *9*, 123. [CrossRef] [PubMed]
23. Luo, H.; Wang, X.; Zhang, R.; Liang, S.; Kang, X.; Zhang, X.; Lou, Q.; Xiong, K.; Yang, J.; Si, L. Rectal Indomethacin and Spraying of Duodenal Papilla with Epinephrine Increases Risk of Pancreatitis Following Endoscopic Retrograde Cholangiopancreatography. *Clin. Gastroenterol. Hepatol.* **2018**. [CrossRef] [PubMed]
24. Lerch, M.; Hoppe-Seyler, P.; Gerok, W. Origin and development of exocrine pancreatic insufficiency in experimental renal failure. *Gut* **1994**, *35*, 401–407. [CrossRef] [PubMed]
25. Yao, S.; Li, J.; Fan, X.; Liu, Q.; Lian, J. The effect of selective serotonin re-uptake inhibitors on risk of type II diabetes mellitus and acute pancreatitis: A meta-analysis. *Biosci. Rep.* **2018**, *38*, BSR20180967. [CrossRef] [PubMed]
26. Singh, R.G.; Pendharkar, S.A.; Cervantes, A.; Cho, J.; Miranda-Soberanis, V.; Petrov, M.S. Abdominal obesity and insulin resistance after an episode of acute pancreatitis. *Dig. Liver Dis.* **2018**, *50*, 1081–1087. [CrossRef] [PubMed]
27. Barreto, S.G. How does cigarette smoking cause acute pancreatitis? *Pancreatology* **2016**, *16*, 157–163. [CrossRef]
28. Schneider, L.; Jabrailova, B.; Soliman, H.; Hofer, S.; Strobel, O.; Hackert, T.; Büchler, M.W.; Werner, J. Pharmacological cholinergic stimulation as a therapeutic tool in experimental necrotizing pancreatitis. *Pancreas* **2014**, *43*, 41–46. [CrossRef]
29. Martins, F.d.O.; Gomes, B.C.; Rodrigues, A.S.; Rueff, J. Genetic susceptibility in acute pancreatitis: Genotyping of GSTM1, GSTT1, GSTP1, CASP7, CASP8, CASP9, CASP10, LTA, TNFRSF1B, and TP53 gene variants. *Pancreas* **2017**, *46*, 71–76. [CrossRef]
30. Khaoula, Y.; Mokni, J.; Feten, A.; Ameni, B.; Chedly, M. Blunt abdominal trauma causing acute pancreatitis: Presentation of the case study. *Pan Afr. Med J.* **2018**, *30*, 126.
31. Vujasinovic, M.; Valente, R.; Maier, P.; von Beckerath, V.; Haas, S.L.; Arnelo, U.; Del Chiaro, M.; Kartalis, N.; Pozzi-Mucelli, R.M.; Fernandez-Moro, C. Diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden. *Pancreatology* **2018**, *18*, 900–904. [CrossRef]
32. Zhang, G.; Feng, J.; Xu, Q.; Huang, H. Double filtration plasmapheresis in treatment of hyperlipidemic acute pancreatitis. *Zhejiang Da Xue Xue Bao Yi Xue Ban* **2008**, *37*, 93–96. [PubMed]
33. Dąbrowski, A.; Konturek, S.J.; Konturek, J.W.; Gabryelewicz, A. Role of oxidative stress in the pathogenesis of caerulein-induced acute pancreatitis. *Eur. J. Pharmacol.* **1999**, *377*, 1–11. [CrossRef]
34. Lampel, M.; Kern, H.F. Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretagogue. *Virchows Arch. A* **1977**, *373*, 97–117. [CrossRef]
35. Niederau, C.; Ferrell, L.D.; Grendell, J.H. Caerulein-Induced Acute Necrotizing Pancreatitis in Mice; Protective Effects of Proglumide Benzotript, and Secretin. *Gastroenterology* **1985**, *88*, 1192–1204. [CrossRef]
36. Wisner, J.; Green, D.; Ferrell, L.; Renner, I. Evidence for a role of oxygen derived free radicals in the pathogenesis of caerulein induced acute pancreatitis in rats. *Gut* **1988**, *29*, 1516–1523. [CrossRef]
37. Hartwig, W.; Schimmel, E.; Hackert, T.; Fortunato, F.; Bergmann, F.; Baczako, A.; Strobel, O.; Büchler, M.W.; Werner, J. A novel animal model of severe pancreatitis in mice and its differences to the rat. *Surgery* **2008**, *144*, 394–403. [CrossRef] [PubMed]
38. Clemons, A.P.; Holstein, D.M.; Galli, A.; Saunders, C. Cerulein-induced acute pancreatitis in the rat is significantly ameliorated by treatment with MEK1/2 inhibitors U0126 and PD98059. *Pancreas* **2002**, *25*, 251–259. [CrossRef]
39. Niederau, C.; Ude, K.; Niederau, M.; Lüthen, R.; Strohmeyer, G.; Ferrell, L.D.; Grendell, J.H. Effects of the seleno-organic substance Ebselen in two different models of acute pancreatitis. *Pancreas* **1991**, *6*, 282–290. [CrossRef]
40. Siveke, J.T.; Lubeseder-Martellato, C.; Lee, M.; Mazur, P.K.; Nakhai, H.; Radtke, F.; Schmid, R.M. Notch signaling is required for exocrine regeneration after acute pancreatitis. *Gastroenterology* **2008**, *134*, 544–555.e543. [CrossRef]
41. Xing, M.; Ni, J.B.; Wan, R.; Tang, M.C.; Hu, Y.L.; Yu, G.; Yin, G.J.; Chen, C.Y.; Fan, Y.T.; Xiao, W.Q. Tetraspanin CD 9 is involved in pancreatic damage during caerulein-induced acute pancreatitis in mice. *J. Dig. Dis.* **2015**, *16*, 43–51. [CrossRef]
42. Jia, R.; Ma, J.; Meng, W.; Wang, N. Dihydromyricetin inhibits caerulin-induced TRAF3-p38 signaling activation and acute pancreatitis response. *Biochem. Biophys. Res. Commun.* **2018**, *503*, 1696–1702. [CrossRef]

43. Venglovecz, V.; Pallagi, P.; Kemény, L.; Balázs, A.; Balla, Z.; Becskeházi, E.; Gál, E.; Zvara, Á.; Puskás, L.; Katalin, B. The Importance of Aquaporin 1 in Pancreatitis and Its Relation to the CFTR Cl-Channel. *Front. Physiol.* **2018**, *9*, 854. [CrossRef]
44. Gao, L.; Lu, G.T.; Lu, Y.Y.; Xiao, W.M.; Mao, W.J.; Tong, Z.H.; Yang, N.; Li, B.Q.; Yang, Q.; Ding, Y.B.; et al. Diabetes aggravates acute pancreatitis possibly via activation of NLRP3 inflammasome in db/db mice. *Am. J. Transl. Res.* **2018**, *10*, 2015–2025.
45. Zhang, L.; Zhang, J.; Shea, K.; Xu, L.; Tobin, G.; Knapton, A.; Sharron, S.; Rouse, R. Autophagy in pancreatic acinar cells in caerulein-treated mice: Immunolocalization of related proteins and their potential as markers of pancreatitis. *Toxicol. Pathol.* **2014**, *42*, 435–457. [CrossRef]
46. Sledzinski, M.; Borkowska, A.; Sielicka-Dudzin, A.; Halon, M.; Wozniak, M.; Spodnik, J.H.; Antosiewicz, A.H.; Antosiewicz, J. Cerulein-Induced Acute Pancreatitis Is Associated With c-Jun NH (2)-Terminal Kinase 1–Dependent Ferritin Degradation and Iron-Dependent Free Radicals Formation. *Pancreas* **2013**, *42*, 1070–1077. [CrossRef]
47. García-Hernández, V.; Sarmiento, N.; Sánchez-Bernal, C.; Matellán, L.; Calvo, J.J.; Sanchez-Yaguee, J. Modulation in the expression of SHP-1, SHP-2 and PTP1B due to the inhibition of MAPKs, cAMP and neutrophils early on in the development of cerulein-induced acute pancreatitis in rats. *Biochim. Biophys. Acta Mol. Basis Dis.* **2014**, *1842*, 192–201. [CrossRef]
48. Liu, R.; Qi, H.; Wang, J.; Wang, Y.; Cui, L.; Wen, Y.; Yin, C. Angiotensin-converting enzyme (ACE and ACE2) imbalance correlates with the severity of cerulein-induced acute pancreatitis in mice. *Exp. Physiol.* **2014**, *99*, 651–663. [CrossRef]
49. Ou, X.; Cheng, Z.; Liu, T.; Tang, Z.; Huang, W.; Szatmary, P.; Zheng, S.; Sutton, R.; Toh, C.H.; Zhang, N. Circulating histone levels reflect disease severity in animal models of acute pancreatitis. *Pancreas* **2015**, *44*, 1089–1095. [CrossRef]
50. Szentkereszty, Z.; Kotan, R.; Kiss, F.; Klarik, Z.; Posan, J.; Furka, I.; Sapy, P.; Miko, I.; Peto, K.; Nemeth, N. Effects of various drugs (flunixin, pentoxifylline, enoxaparin) modulating micro-rheological changes in cerulein-induced acute pancreatitis in the rat. *Clin. Hemorheol. Microcirc.* **2014**, *57*, 303–314.
51. Cao, J.; Liu, Q. Protective effects of sivelestat in a caerulein-induced rat acute pancreatitis model. *Inflammation* **2013**, *36*, 1348–1356. [CrossRef]
52. Bae, G.-S.; Heo, K.-H.; Park, K.-C.; Choi, S.B.; Jo, I.-J.; Seo, S.-H.; Kim, D.-G.; Shin, J.-Y.; Kang, D.-G.; Lee, H.-S. Apamin attenuated cerulein-induced acute pancreatitis by inhibition of JNK pathway in mice. *Dig. Dis. Sci.* **2013**, *58*, 2908–2917. [CrossRef]
53. Huang, W.; Cash, N.; Wen, L.; Szatmary, P.; Mukherjee, R.; Armstrong, J.; Chvanov, M.; Tepikin, A.V.; Murphy, M.P.; Sutton, R. Effects of the mitochondria-targeted antioxidant mitoquinone in murine acute pancreatitis. *Mediat. Inflamm.* **2015**, *2015*, 901780. [CrossRef]
54. Huang, W.; Cane, M.C.; Mukherjee, R.; Szatmary, P.; Zhang, X.; Elliott, V.; Ouyang, Y.; Chvanov, M.; Latawiec, D.; Wen, L. Caffeine protects against experimental acute pancreatitis by inhibition of inositol 1, 4, 5-trisphosphate receptor-mediated Ca^{2+} release. *Gut* **2017**, *66*, 301–313. [CrossRef]
55. Schick, V.; Scheiber, J.A.; Mooren, F.C.; Turi, S.; Ceyhan, G.O.; Schnekenburger, J.; Sendler, M.; Schwaiger, T.; Omercevic, A.; van den Brandt, C. Effect of magnesium supplementation and depletion on the onset and course of acute experimental pancreatitis. *Gut* **2014**, *63*, 1469–1480. [CrossRef]
56. Wang, Y.Z.; Zhang, Y.C.; Cheng, J.S.; Ni, Q.; Li, P.J.; Wang, S.W.; Han, W.; Zhang, Y.L. BML-111, a lipoxin receptor agonist, ameliorates 'two-hit'-induced acute pancreatitis-associated lung injury in mice by the upregulation of heme oxygenase-1. *Artif. Cells Nanomed. Biotechnol.* **2014**, *42*, 110–120. [CrossRef]
57. Weng, T.-I.; Wu, H.-Y.; Chen, B.-L.; Jhuang, J.-Y.; Huang, K.-H.; Chiang, C.-K.; Liu, S.-H. C/EBP homologous protein deficiency aggravates acute pancreatitis and associated lung injury. *World J. Gastroenterol.* **2013**, *19*, 7097–7105. [CrossRef]
58. Marciniak, A.; Walczyna, B.; Rajtar, G.; Marciniak, S.; Wojtak, A.; Lasiecka, K. Tempol, a membrane-permeable radical scavenger, exhibits anti-inflammatory and cardioprotective effects in the cerulein-induced pancreatitis rat model. *Oxidative Med. Cell. Longev.* **2016**, *2016*, 4139851. [CrossRef]
59. Bartholomew, C. Acute scorpion pancreatitis in Trinidad. *Br. Med. J.* **1970**, *1*, 666–668. [CrossRef]
60. Marsh, W.H.; Vukov, G.A.; Conradi, E.C. Acute pancreatitis after cutaneous exposure to an organophosphate insecticide. *Am. J. Gastroenterol.* **1988**, *83*, 1158–1160.
61. Steer, M.L.; Meldolesi, J. The cell biology of experimental pancreatitis. *N. Engl. J. Med.* **1987**, *316*, 144–150.

62. Steer, M.L. Frank Brooks memorial Lecture: The early intraacinar cell events which occur during acute pancreatitis. *Pancreas* **1998**, *17*, 31–37. [CrossRef]
63. Norberg, K.J.; Nania, S.; Li, X.; Gao, H.; Szatmary, P.; Segersvärd, R.; Haas, S.; Wagman, A.; Arnelo, U.; Sutton, R. RCAN1 is a marker of oxidative stress, induced in acute pancreatitis. *Pancreatology* **2018**, *18*, 734–741. [CrossRef]
64. García-Hernández, V.; Sánchez-Bernal, C.; Schvartz, D.; Calvo, J.J.; Sanchez, J.-C.; Sánchez-Yagüe, J. A tandem mass tag (TMT) proteomic analysis during the early phase of experimental pancreatitis reveals new insights in the disease pathogenesis. *J. Proteom.* **2018**, *181*, 190–200. [CrossRef]
65. Tang, M.; Hu, G.; Zhao, Y.; Su, M.; Wang, Y.; Jia, W.; Qiu, Y.; Liu, G.; Wang, X. A serum metabolomic investigation on lipoprotein lipase-deficient mice with hyperlipidemic pancreatitis using gas chromatography/mass spectrometry. *Biomed. Rep.* **2013**, *1*, 469–473. [CrossRef]
66. Cai, Y.; Shen, Y.; Xu, G.; Tao, R.; Yuan, W.; Huang, Z.; Zhang, D. TRAM1 protects AR42J cells from caerulein-induced acute pancreatitis through ER stress-apoptosis pathway. *In Vitro Cell. Dev. Biol. Anim.* **2016**, *52*, 530–536. [CrossRef]
67. Terao, K.; Wake, H.; Adachi, N.; Liu, K.; Teshigawara, K.; Takahashi, H.; Mori, S.; Nishibori, M. Histidine-Rich Glycoprotein Suppresses Hyperinflammatory Responses of Lung in a Severe Acute Pancreatitis Mouse Model. *Pancreas* **2018**, *47*, 1156–1164. [CrossRef]
68. Sun, K.; He, S.-B.; Qu, J.-G.; Dang, S.-C.; Chen, J.-X.; Gong, A.-H.; Xie, R.; Zhang, J.-X. IRF5 regulates lung macrophages M2 polarization during severe acute pancreatitis in vitro. *World J. Gastroenterol.* **2016**, *22*, 9368. [CrossRef]
69. Sun, J.; Fu, J.; Zhong, Y.; Li, L.; Chen, C.; Wang, X.; Wang, L.; Hou, Y.; Wang, H.; Zhao, R. NRF2 mitigates acute alcohol-induced hepatic and pancreatic injury in mice. *Food Chem. Toxicol.* **2018**, *121*, 495–503. [CrossRef]
70. Huang, W.; Booth, D.M.; Cane, M.C.; Chvanov, M.; Javed, M.A.; Elliott, V.L.; Armstrong, J.A.; Dingsdale, H.; Cash, N.; Li, Y. Fatty acid ethyl ester synthase inhibition ameliorates ethanol-induced Ca^{2+}-dependent mitochondrial dysfunction and acute pancreatitis. *Gut* **2014**, *63*, 1313–1324. [CrossRef]
71. Schneider, L.; Dieckmann, R.; Hackert, T.; Gebhard, M.-M.; Werner, J. Acute alcohol-induced pancreatic injury is similar with intravenous and intragastric routes of alcohol administration. *Pancreas* **2014**, *43*, 69–74. [CrossRef]
72. Kiziler, A.R.; Aydemir, B.; Gulyasar, T.; Unal, E.; Gunes, P. Relationships among iron, protein oxidation and lipid peroxidation levels in rats with alcohol-induced acute pancreatitis. *Biol. Trace Elem. Res.* **2008**, *124*, 135–143. [CrossRef]
73. Kui, B.; Balla, Z.; Vasas, B.; Végh, E.T.; Pallagi, P.; Kormányos, E.S.; Venglovecz, V.; Iványi, B.; Takács, T.; Hegyi, P. New insights into the methodology of L-arginine-induced acute pancreatitis. *PLoS ONE* **2015**, *10*, e0117588. [CrossRef]
74. Tashiro, M.; Schäfer, C.; Yao, H.; Ernst, S.; Williams, J. Arginine induced acute pancreatitis alters the actin cytoskeleton and increases heat shock protein expression in rat pancreatic acinar cells. *Gut* **2001**, *49*, 241–250. [CrossRef]
75. Le, T.; Eisses, J.F.; Lemon, K.L.; Ozolek, J.A.; Pociask, D.A.; Orabi, A.I.; Husain, S.Z. Intra-ductal infusion of taurocholate followed by distal common bile duct ligation leads to a severe, necrotic model of pancreatitis in mice. *Pancreas* **2015**, *44*, 493–499.
76. Zhao, Q.; Zhang, H.; Huang, J.; Yu, H.; Li, J.; Che, Q.; Sun, Y.; Jin, Y.; Wu, J. Melatonin attenuates the inflammatory response via inhibiting the C/EBP homologous protein-mediated pathway in taurocholate-induced acute pancreatitis. *Int. J. Mol. Med.* **2018**, *42*, 3513–3521. [CrossRef]
77. Aho, H.; Koskensalo, S.-L.; Nevalainen, T. Experimental pancreatitis in the rat: Sodium taurocholate-induced acute haemorrhagic pancreatitis. *Scand. J. Gastroenterol.* **1980**, *15*, 411–416. [CrossRef]
78. Hua, J.; He, Z.-G.; Qian, D.-H.; Lin, S.-P.; Gong, J.; Meng, H.-B.; Yang, T.-S.; Sun, W.; Xu, B.; Zhou, B. Angiopoietin-1 gene-modified human mesenchymal stem cells promote angiogenesis and reduce acute pancreatitis in rats. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 3580–3595.
79. Kim, H.-W.; Song, W.-J.; Li, Q.; Han, S.-M.; Jeon, K.-O.; Park, S.-C.; Ryu, M.-O.; Chae, H.-K.; Kyeong, K.; Youn, H.-Y. Canine adipose tissue-derived mesenchymal stem cells ameliorate severe acute pancreatitis by regulating T cells in rats. *J. Vet. Sci.* **2016**, *17*, 539–548. [CrossRef]

80. Uysal, B.; Yasar, M.; Ersoz, N.; Coskun, O.; Kilic, A.; Cayc, T.; Kurt, B.; Oter, S.; Korkmaz, A.; Guven, A. Efficacy of hyperbaric oxygen therapy and medical ozone therapy in experimental acute necrotizing pancreatitis. *Pancreas* **2010**, *39*, 9–15. [CrossRef]
81. Andrzejewska, A.; Dlugosz, J.; Jurkowska, G. The effect of antecedent acute ethanol ingestion on the pancreas ultrastructure in taurocholate pancreatitis in rats. *Exp. Mol. Pathol.* **1998**, *65*, 64–77. [CrossRef]
82. Pandol, S.J.; Periskic, S.; Gukovsky, I.; Zaninovic, V.; Jung, Y.; Zong, Y.; Solomon, T.E.; Gukovskaya, A.S.; Tsukamoto, H. Ethanol diet increases the sensitivity of rats to pancreatitis induced by cholecystokinin octapeptide. *Gastroenterology* **1999**, *117*, 706–716. [CrossRef]
83. Foitzik, T.; Lewandrowski, K.B.; Fernández-del Castillo, C.; Rattner, D.W.; Klar, E.; Warshaw, A.L. Exocrine hyperstimulation but not pancreatic duct obstruction increases the susceptibility to alcohol-related pancreatic injury. *Arch. Surg.* **1994**, *129*, 1081–1085. [CrossRef]
84. Vonlaufen, A. Modeling alcoholic pancreatitis by ethanol feeding and lipopolysaccharide (LPS) challenge. *Pancreapedia Exocrine Pancreas Knowl. Base* **2011**. [CrossRef]
85. Javed, M.A.; Wen, L.; Awais, M.; Latawiec, D.; Huang, W.; Chvanov, M.; Schaller, S.; Bordet, T.; Michaud, M.; Pruss, R. TRO40303 Ameliorates Alcohol-Induced Pancreatitis Through Reduction of Fatty Acid Ethyl Ester–Induced Mitochondrial Injury and Necrotic Cell Death. *Pancreas* **2018**, *47*, 18–24. [CrossRef]
86. Schneider, A.; Whitcomb, D.C.; Singer, M.V. Animal models in alcoholic pancreatitis–what can we learn? *Pancreatology* **2002**, *2*, 189–203. [CrossRef]
87. Siech, M.; Weber, H.; Letko, G.; Dummler, W.; Schoenberg, M.; Beger, H. Similar morphological and intracellular biochemical changes in alcoholic acute pancreatitis and ischemic acute pancreatitis in rats. *Pancreas* **1997**, *14*, 32–38. [CrossRef]
88. Hall, B.; Limaye, A.; Kulkarni, A.B. Overview: Generation of gene knockout mice. *Curr. Protoc. Cell Biol.* **2009**, *44*, 19.12.1–19.12.17.
89. Capecchi, M.R. Targeted gene replacement. *Sci. Am.* **1994**, *270*, 52–59. [CrossRef]
90. Tesson, L.; Cozzi, J.; Menoret, S.; Remy, S.; Usal, C.; Fraichard, A.; Anegon, I. Transgenic modifications of the rat genome. *Transgenic Res.* **2005**, *14*, 531–546. [CrossRef]
91. Zan, Y.; Haag, J.D.; Chen, K.-S.; Shepel, L.A.; Wigington, D.; Wang, Y.-R.; Hu, R.; Lopez-Guajardo, C.C.; Brose, H.L.; Porter, K.I. Production of knockout rats using ENU mutagenesis and a yeast-based screening assay. *Nat. Biotechnol.* **2003**, *21*, 645–651. [CrossRef]
92. Tao, L.; Lin, X.; Tan, S.; Lei, Y.; Liu, H.; Guo, Y.; Zheng, F.; Wu, B. β-Arrestin1 alleviates acute pancreatitis via repression of NF-κBp65 activation. *J. Gastroenterol. Hepatol.* **2019**, *34*, 284–292. [CrossRef]
93. Norkina, O.; Graf, R.; Appenzeller, P.; De Lisle, R.C. Caerulein-induced acute pancreatitis in mice that constitutively overexpress Reg/PAP genes. *BMC Gastroenterol.* **2006**, *6*, 16. [CrossRef]
94. Jancsó, Z.; Hegyi, E.; Sahin-Tóth, M. Chymotrypsin Reduces the Severity of Secretagogue-Induced Pancreatitis in Mice. *Gastroenterology* **2018**, *155*, 1017–1021. [CrossRef]
95. Yu, J.; Ni, L.; Zhang, X.; Zhang, J.; Abdel-Razek, O.; Wang, G. Surfactant Protein D Dampens Lung Injury by Suppressing NLRP3 Inflammasome Activation and NF-κB Signaling in Acute Pancreatitis. *Shock* **2019**, *51*, 557–568. [CrossRef]
96. Zhao, Q.; Wei, Y.; Pandol, S.J.; Li, L.; Habtezion, A. STING Signaling Promotes Inflammation in Experimental Acute Pancreatitis. *Gastroenterology* **2018**, *154*, 1822–1835.e2. [CrossRef]
97. Farber, E.; Popper, H. Production of acute pancreatitis with ethionine and its prevention by methionine. *Proc. Soc. Exp. Biol. Med.* **1950**, *74*, 838–844. [CrossRef]
98. Lombardi, B.; Rao, N.K. Acute hemorrhagic pancreatic necrosis in mice. Influence of the age and sex of the animals and of dietary ethionine, choline, methionine, and adenine sulfate. *Am. J. Pathol.* **1975**, *81*, 87.
99. Kui, B.; Balla, Z.; Végh, E.T.; Pallagi, P.; Venglovecz, V.; Iványi, B.; Takács, T.; Hegyi, P.; Rakonczay, Z., Jr. Recent advances in the investigation of pancreatic inflammation induced by large doses of basic amino acids in rodents. *Lab. Investig.* **2014**, *94*, 138–149. [CrossRef]
100. Gilliland, L.; Steer, M. Effects of ethionine on digestive enzyme synthesis and discharge by mouse pancreas. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **1980**, *239*, G418–G426. [CrossRef]
101. Akita, S.; Kubota, K.; Kobayashi, A.; Misawa, R.; Shimizu, A.; Nakata, T.; Yokoyama, T.; Takahashi, M.; Miyagawa, S. Role of bone marrow cells in the development of pancreatic fibrosis in a rat model of pancreatitis induced by a choline-deficient/ethionine-supplemented diet. *Biochem. Biophys. Res. Commun.* **2012**, *420*, 743–749. [CrossRef]

102. Nagao, S.; Taguchi, K.; Sakai, H.; Yamasaki, K.; Watanabe, H.; Otagiri, M.; Maruyama, T. Carbon monoxide-bound hemoglobin vesicles ameliorate multiorgan injuries induced by severe acute pancreatitis in mice by their anti-inflammatory and antioxidant properties. *Int. J. Nanomed.* **2016**, *11*, 5611–5620. [CrossRef]
103. Mizunuma, T.; Kawamura, S.; Kishino, Y. Effects of injecting excess arginine on rat pancreas. *J. Nutr.* **1984**, *114*, 467–471. [CrossRef]
104. Ou, X.; Hua, Y.; Liao, X.; Gong, C.; Kang, Y. Cognitive impairments induced by severe acute pancreatitis are attenuated by berberine treatment in rats. *Mol. Med. Rep.* **2018**, *18*, 3437–3444. [CrossRef]
105. Tani, S.; Itoh, H.; Okabayashi, Y.; Nakamura, T.; Fujii, M.; Fujisawa, T.; Koide, M.; Otsuki, M. New model of acute necrotizing pancreatitis induced by excessive doses of arginine in rats. *Dig. Dis. Sci.* **1990**, *35*, 367–374. [CrossRef]
106. Uçmak, F.; Ekin, N.; İbiloğlu, İ.; Arslan, S.; Kaplan, İ.; Şenateş, E. Prophylactic Administration of Silybin Ameliorates L-Arginine-Induced Acute Pancreatitis. *Med Sci. Monit. Int. Med J. Exp. Clin. Res.* **2016**, *22*, 3641–3646. [CrossRef]
107. Saka, M.; Tuzun, A.; Ates, Y.; Bagci, S.; Karaeren, N.; Dagalp, K. Acute pancreatitis possibly due to arginine use: A case report. *Turk. J. Gastroenterol.* **2004**, *15*, 56–58.
108. Binet, Q.; Dufour, I.; Agneessens, E.; Debongnie, J.-C.; Aouattah, T.; Covas, A.; Coche, J.-C.; De Koninck, X. The second case of a young man with l-arginine-induced acute pancreatitis. *Clin. J. Gastroenterol.* **2018**, *11*, 424–427. [CrossRef]
109. Seidel, H. Bemerkungen zu meiner Methode der experimentellen Erzeugung der akuten hämorrhagischen Pankreatitis. *Zentralbl Chir* **1910**, *37*, 1601–1604.
110. Dickson, A.; Foulis, A.; Imrie, C. Histology and bacteriology of closed duodenal loop models of experimental acute pancreatitis in the rat. *Digestion* **1986**, *34*, 15–21. [CrossRef]
111. Adler, G. Experimental models and concepts in acute pancreatitis. *Exocrine Pancreas Biol. Pathobiol. Dis.* **1986**, 407–421.
112. Nevalainen, T.; Seppä, A. Acute pancreatitis caused by closed duodenal loop in the rat. *Scand. J. Gastroenterol.* **1975**, *10*, 521–527.
113. Chetty, U.; Gilmour, H.; Taylor, T. Experimental acute pancreatitis in the rat—A new model. *Gut* **1980**, *21*, 115–117. [CrossRef]
114. Orda, R.; Hadas, N.; Orda, S.; Wiznitzer, T. Experimental acute pancreatitis: Inducement by taurocholate sodium-trypsin injection into a temporarily closed duodenal loop in the rat. *Arch. Surg.* **1980**, *115*, 327–329. [CrossRef]
115. Deitch, E.A.; Sittig, K.; Li, M.; Berg, R.; Specian, R.D. Obstructive jaundice promotes bacterial translocation from the gut. *Am. J. Surg.* **1990**, *159*, 79–84. [CrossRef]
116. Nieuwenhuijs, V.B.; van Dijk, J.E.; Gooszen, H.G.; Akkermans, L.M. Obstructive jaundice, bacterial translocation and interdigestive small-bowel motility in rats. *Digestion* **2000**, *62*, 255–261. [CrossRef]
117. Sugimoto, M.; Takada, T.; Yasuda, H. A new experimental pancreatitis by incomplete closed duodenal loop: The influence of pancreatic microcirculation on the development and progression of induced severe pancreatitis in rats. *Pancreas* **2004**, *28*, e112–e119. [CrossRef]
118. Savu, A.; Savu, B.; Luca, C.; Mihaila, D.; Toma, O.; Crauciuc, E. Experimental models of acute pancreatitis-closed duodenal loop mode. *Analele Stiintifice ale Universitatii" Al. I. Cuza" Din Iasi.* **2009**, *10*, 83–88.
119. Reber, H.A.; Roberts, C.; Way, L.W. The pancreatic duct mucosal barrier. *Am. J. Surg.* **1979**, *137*, 128–134. [CrossRef]
120. Cen, Y.; Liu, C.; Li, X.; Yan, Z.; Kuang, M.; Su, Y.; Pan, X.; Qin, R.; Liu, X.; Zheng, J. Artesunate ameliorates severe acute pancreatitis (SAP) in rats by inhibiting expression of pro-inflammatory cytokines and Toll-like receptor 4. *Int. Immunopharmacol.* **2016**, *38*, 252–260. [CrossRef]
121. Aho, H.; Nevalainen, T.; Aho, A. Experimental pancreatitis in the rat. Development of pancreatic necrosis, ischemia and edema after intraductal sodium taurocholate injection. *Eur. Surg. Res. Eur. Chir. Forsch. Rech. Chir. Eur.* **1983**, *15*, 28–36.
122. Unal, E.; Atalay, S.; Tolan, H.K.; Yuksekdag, S.; Yucel, M.; Acar, A.; Basak, F.; Gunes, P.; Bas, G. Biliopancreatic duct injection of ethanol as an experimental model of acute and chronic pancreatitis in rats. *Int. J. Clin. Exp. Med.* **2015**, *8*, 304–310.

123. Lu, F.; Wang, F.; Chen, Z.; Huang, H. Effect of mesenchymal stem cells on small intestinal injury in a rat model of acute necrotizing pancreatitis. *Stem Cell Res. Ther.* **2017**, *8*, 12. [CrossRef]
124. Liu, Z.-H.; Peng, J.-S.; Li, C.-J.; Yang, Z.-L.; Xiang, J.; Song, H.; Wu, X.-B.; Chen, J.-R.; Diao, D.-C. A simple taurocholate-induced model of severe acute pancreatitis in rats. *World J. Gastroenterol.* **2009**, *15*, 5732–5739. [CrossRef]
125. Zhu, R.; Zhao, Y.; Li, X.; Bai, T.; Wang, S.; Wang, W.; Sun, Y. Effects of penehyclidine hydrochloride on severe acute pancreatitis-associated acute lung injury in rats. *Biomed. Pharmacother.* **2018**, *97*, 1689–1693. [CrossRef]
126. Shi, C.; Hou, C.; Zhu, X.; Huang, D.; Peng, Y.; Tu, M.; Li, Q.; Miao, Y. SRT1720 ameliorates sodium taurocholate-induced severe acute pancreatitis in rats by suppressing NF-κB signalling. *Biomed. Pharmacother.* **2018**, *108*, 50–57. [CrossRef]
127. Huang, L.; Jiang, Y.; Sun, Z.; Gao, Z.; Wang, J.; Zhang, D. Autophagy strengthens intestinal mucosal barrier by attenuating oxidative stress in severe acute pancreatitis. *Dig. Dis. Sci.* **2018**, *63*, 910–919. [CrossRef]
128. Zheng, J.; Xu, H.; Huang, C.; Fan, J.; Mei, Q.; Lu, Y.; Lou, L.; Wang, X.; Zeng, Y. Quercetin protects against intestinal barrier disruption and inflammation in acute necrotizing pancreatitis through TLR4/MyD88/p38 MAPK and ERS inhibition. *Pancreatology* **2018**, *18*, 742–752.
129. Zhang, Y.-M.; Zhu, L.; Zhao, X.-L.; Chen, H.; Kang, H.-X.; Zhao, J.-L.; Wan, M.-H.; Li, J.; Zhu, L.; Tang, W.-F. Optimal timing for the oral administration of Da-Cheng-Qi decoction based on the pharmacokinetic and pharmacodynamic targeting of the pancreas in rats with acute pancreatitis. *World J. Gastroenterol.* **2017**, *23*, 7098–7109. [CrossRef]
130. Yan, L.; Li, Q.F.; Rong, Y.T.; Chen, Y.H.; Huang, Z.H.; Wang, Z.Z.; Peng, J. The protective effects of rutaecarpine on acute pancreatitis. *Oncol. Lett.* **2018**, *15*, 3121–3126. [CrossRef]
131. Zhang, X.-P.; Li, Z.-J.; Zhang, J. Inflammatory mediators and microcirculatory disturbance in acute pancreatitis. *Hepatobiliary Pancreat. Dis. Int.* **2009**, *8*, 351–357.
132. Pfeffer, R.B.; Lazzarini-Robertson, A.; Safadi, D.; Mixter, G.; Secoy, C.F.; Hinton, J.W. Gradations of pancreatitis, edematous, through hemorrhagic, experimentally produced by controlled injection of microspheres into blood vessels in dogs. *Surgery* **1962**, *51*, 764–769.
133. Lasson, Å.; Ohlsson, K. Consumptive coagulopathy, fibrinolysis and protease antiprotease interactions during acute human pancreatitis. *Thromb. Res.* **1986**, *41*, 167–183. [CrossRef]
134. Liu, L.; Li, Y.; Fan, L.; Zhao, Q.; Wang, D.; Cheng, S.; Zhang, A.; Qin, Y.; Zhang, B. Effect of vascular bradykinin on pancreatic microcirculation and hemorheology in rats with severe acute pancreatitis. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 2646–2650.
135. Spormann, H.; Sokolowski, A.; Birkigt, H.; Letko, G. Contribution of pancreatic edema and short-term ischemia to experimental acute pancreatitis in the rat. I. Procedure and pathomorphological investigations. *Zeitschrift fur Experimentelle Chirurgie Transplantation und Kunstliche Organe Organ der Sektion Experimentelle Chirurgie der Gesellschaft fur Chirurgie der DDR* **1986**, *19*, 323–330.
136. Sjövall, S.; Holmin, T.; Evander, A.; Stenram, U. Splenic and gastro-duodenal vein occlusion—Influence on the pancreatic gland and on the outcome of experimental pancreatitis. *Int. J. Pancreatol.* **1988**, *3*, 143–149.
137. Hoffmann, T.; Leiderer, R.; Waldner, H.; Arbogast, S.; Messmer, K. Ischemia reperfusion of the pancreas: A new in vivo model for acute pancreatitis in rats. *Res. Exp. Med.* **1995**, *195*, 125–144. [CrossRef]
138. Dembinski, A.; Warzecha, Z.; Ceranowicz, P.; Stachura, J.; Tomaszewska, R.; Konturek, S.; Sendur, R.; Dembinski, M.; Pawlik, W. Pancreatic damage and regeneration in the course of ischemia-reperfusion induced pancreatitis in rats. *J. Physiol. Pharmacol.* **2001**, *52*, 221–235.
139. Bukowczan, J.; Warzecha, Z.; Ceranowicz, P.; Kuśnierz-Cabala, B.; Tomaszewska, R. Obestatin accelerates the recovery in the course of ischemia/reperfusion-induced acute pancreatitis in rats. *PLoS ONE* **2015**, *10*, e0134380. [CrossRef]
140. Bukowczan, J.; Warzecha, Z.; Ceranowicz, P.; Kusnierz-Cabala, B.; Tomaszewska, R.; Dembinski, A. Therapeutic effect of ghrelin in the course of ischemia/reperfusion-induced acute pancreatitis. *Curr. Pharm. Des.* **2015**, *21*, 2284–2290. [CrossRef]
141. Schanaider, A.; de Carvalho, T.P.; de Oliveira Coelho, S.; Renteria, J.M.; Eleuthério, E.C.A.; Castelo-Branco, M.T.L.; Madi, K.; Baetas-da-Cruz, W.; de Souza, H.S.P. Ischemia–reperfusion rat model of acute pancreatitis: Protein carbonyl as a putative early biomarker of pancreatic injury. *Clin. Exp. Med.* **2015**, *15*, 311–320. [CrossRef]

142. Churg, A.; Richter, W. Early changes in the exocrine pancreas of the dog and rat after ligation of the pancreatic duct. A light and electron microscopic study. *Am. J. Pathol.* **1971**, *63*, 521–546.
143. Buchwalow, I.; Schnekenburger, J.; Atiakshin, D.; Samoilova, V.; Wolf, E.; Boecker, W.; Tiemann, K. Oxidative stress and NO generation in the rat pancreatitis induced by pancreatic duct ligation. *Acta Histochem.* **2017**, *119*, 252–256. [CrossRef]
144. Baxter, J.; Jenkins, S.; Day, D.; Roberts, N.; Cowell, D.; Mackie, C.; Shields, R. Effects of somatostatin and a long-acting somatostatin analogue on the prevention and treatment of experimentally induced acute pancreatitis in the rat. *Br. J. Surg.* **1985**, *72*, 382–385. [CrossRef]
145. Buscail, L.; Sénégas-Balas, F.; Balas, D.; Bouisson, M.; Bertrand, C.; Ribet, A. Protective effect of misoprostol, a synthetic prostaglandin E1 analog, on experimental pancreatitis induced by pancreatic duct ligation in rat. *Pancreas* **1989**, *4*, 715–723. [CrossRef]
146. Ohshio, G.; Saluja, A.; Steer, M. Effects of short-term pancreatic duct obstruction in rats. *Gastroenterology* **1991**, *100*, 196–202. [CrossRef]
147. Cohen, D.B.; Magnotti, L.J.; Lu, Q.; Xu, D.Z.; Berezina, T.L.; Zaets, S.B.; Alvarez, C.; Machiedo, G.; Deitch, E.A. Pancreatic duct ligation reduces lung injury following trauma and hemorrhagic shock. *Ann. Surg.* **2004**, *240*, 885–891. [CrossRef]
148. De-Madaria, E.; Martínez, J.F.; Aparicio, J.R.; Lluís, F. Aggressive Fluid Resuscitation in Acute Pancreatitis: In Aqua Sanitas? *Am. J. Gastroenterol.* **2017**, *112*, 1617–1618. [CrossRef]
149. De-Madaria, E.; Herrera-Marante, I.; González-Camacho, V.; Bonjoch, L.; Quesada-Vázquez, N.; Almenta-Saavedra, I.; Miralles-Maciá, C.; Acevedo-Piedra, N.G.; Roger-Ibáñez, M.; Sánchez-Marin, C. Fluid resuscitation with lactated Ringer's solution vs normal saline in acute pancreatitis: A triple-blind, randomized, controlled trial. *United Eur. Gastroenterol. J.* **2018**, *6*, 63–72. [CrossRef]
150. Singh, V.P. High on drugs: Lessons from opiates in pancreatitis. *Gut* **2018**, *67*, 600–602. [CrossRef]
151. Zhang, J.; Zhu, S.; Tan, D.; Ma, A.; Yang, Y.; Xu, J. A meta-analysis of early oral refeeding and quickly increased diet for patients with mild acute pancreatitis. *Saudi J. Gastroenterol. Off. J. Saudi Gastroenterol. Assoc.* **2019**, *25*, 14–19.
152. Van Brunschot, S.; van Grinsven, J.; van Santvoort, H.C.; Bakker, O.J.; Besselink, M.G.; Boermeester, M.A.; Bollen, T.L.; Bosscha, K.; Bouwense, S.A.; Bruno, M.J. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: A multicentre randomised trial. *Lancet* **2018**, *391*, 51–58. [CrossRef]