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FLUID PHASE ENDOCYTOSIS IN PANCREATIC ACINAR CELLS: AN EARLY EVENT IN ALCOHOLIC CHRONIC PANCREATITIS

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Abstract: *Chronic pancreatitis (CP) affects approximately 34 per 100,000 people globally, with alcoholic chronic pancreatitis (ACP) being the most prevalent form in regions with high alcohol consumption, accounting for 40–70% of cases. This study explores fluid-phase endocytosis as a potential early trigger in ACP pathogenesis, highlighting its role in intracellular stress. It also investigates the link between pancreatic and hepatic dysfunction in an alcohol-induced mouse model through analysis of key biochemical markers. Swiss Albino mice (n=5/group) were divided into control, ethanol, and ethanol-cerulein groups, with the latter two receiving ethanol (3 g/kg, IP, twice daily, six days/week, for six weeks), and the ethanol-cerulein group additionally receiving weekly cerulein injections (50 µg/kg, hourly ×7) while control group received an equivalent volume of isotonic saline instead of ethanol and cerulein. At the end of the experimental period, blood samples were collected for biochemical assays, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), amylase and lipase (U/l), and gamma-glutamyl transferase (Gamma GT) (U/l). Pancreatic acinar cells were isolated for fluid-phase endocytosis assessment, and pancreatic sections were stained with hematoxylin and eosin for histological analysis. Results showed a significant elevation in biochemical parameters, enhanced endocytic activity, and acinar loss with glandular atrophy in the ethanol+ cerulein group compared to controls and ethanol treated group. The study highlighted an increase in fluid-phase endocytosis, particularly in the ethanol+ cerulein-treated group, as evidenced by the enhanced uptake of Texus Red-Dextran-labeled structures. This suggests that the combination of ethanol and cerulein not only induces biochemical changes but also significantly alters cellular processes, such as endocytosis, which may contribute to the observed pancreatic damage.*

Introduction

Chronic pancreatitis is a progressive inflammatory condition of the pancreas that leads to irreversible structural and functional deterioration (Mann et al., 2021). Acute pancreatitis occurs when inflammation arises suddenly and resolves within a short duration. In contrast, chronic pancreatitis persists for months or even years, leading to permanent tissue damage. The disease is characterized by fibrosis, pancreatic insufficiency, and the formation of calcium stones or cysts, which can obstruct the pancreatic duct, reducing enzyme and hormone secretion (Mann et al., 2021). This disruption impairs digestion, glucose regulation, and increases the risk of malnutrition and diabetes. The primary clinical manifestations include abdominal pain and Pancreatic insufficiency.

Advancements in molecular and genomic research, along with improved pancreatic imaging, have provided significant insights into the genetic, environmental, immunological, and pathological factors contributing to chronic pancreatitis (Zator andWhitcomb,2017). The Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive (TIGAR-O) classification system identifies major risk factors (Whitcomb and North American Pancreatitis Study Group, 2019), and genetic studies have highlighted the role of trypsin activation in disease progression, with mutations in PRSS1, SPINK1, and CTRC genes promoting excessive trypsin activity (Choudarietal.,2004;Gargetal.,2009;Ballardetal.,

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2015). Single nucleotide polymorphisms (SNPs) at PRSS1–PRSS2 and CLDN2–MORC4 loci are associated with chronic pancreatitis, particularly in alcohol-induced cases.

Excessive alcohol consumption is a well-documented risk factor for both acute and chronic pancreatitis, with alcoholics being at a significantly higher risk (Samokhvalov et al., 2015). Mitochondrial dysfunction plays a central role in alcohol-induced pancreatic injury, leading to energy deficits and oxidative stress due to the pancreas's high protein synthesis demand. Structural abnormalities in mitochondria contribute to acinar cell dysfunction.

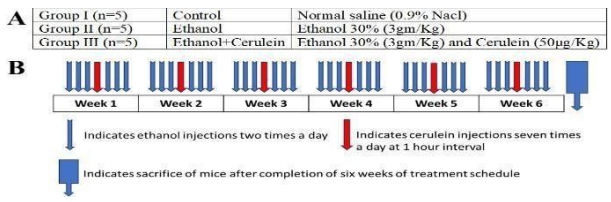
Alcohol consumption exacerbates these morphological and biochemical alterations. Fatty acid ethyl esters (FAEEs), produced through alcohol metabolism, contribute to pancreatic damage by disrupting mitochondrial function, elevating cytosolic calcium levels, and inducing necrosis in acinar cells (Jakkampudi et al., 2020). Chronic pancreatitis is marked by exocrine dysfunction in its early stages, with diabetes mellitus manifesting later (Mohapatra et al., 2016). Acinar cell apoptosis and increased Rb protein expression play critical roles in pancreatic tissue loss (Barrera et al., 2018). Supramaximal stimulation of acinar cells leads to lysosomal enzyme activation, vacuole formation, and progressive destruction (Sendler et al., 2016). Given these underlying mechanisms, our study aims to investigate the functionality of endocytic vesicles in the development of chronic pancreatitis, providing new insights into disease progression.

This study aims to investigate the role of fluid-phase endocytosis as a potential early event in the pathogenesis of alcohol-induced chronic pancreatitis. Additionally, it examines the co-occurrence of pancreatic and hepatic dysfunction in an alcohol-induced chronic pancreatitis mouse model by assessing biochemical markers of pancreatic and liver function. Insights gained from this research will contribute to a better understanding of the underlying mechanisms and may aid in the development of targeted therapeutic strategies.

Methodology

Animals

All studies were conducted on male Swiss Albino mice (25–30g, 2 weeks old) under IAEC-approved ethical conditions in a pathogen-free, temperature (25 ± 2 °C) and humidity-controlled room with a 12 h light cycle. Mice had free access to food and water and were fed a standard laboratory diet (71%carbohydrate, 18% protein, 7% fat, 4% salts) for a week before treatment. All animal experiments were carried out in accordance with the Institutional Animal Ethics Committee's (IAEC)ethical guidelines and approved by IAEC of Serampore



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Experimental design and chronic pancreatitis induction

The research design and animal grouping are illustrated in Figure 1. Briefly, mice were randomly divided into three groups (n=5): Control, Ethanol, and Ethanol-Cerulein. The Ethanol and Ethanol-Cerulein groups received two intraperitoneal (IP) injections of 150 µL (3 g/kg) of 30% ethanol at 10 a.m. and 6p.m., six days a week for six weeks. Additionally, the Ethanol-Cerulein group received seven IP injections of cerulein (50 µg/kg; Sigma Aldrich, USA) at hourly intervals, one day per week (Ahmadietal.,2016). The Control group received an equivalent volume of isotonic saline instead of ethanol and cerulein. All mice were sacrificed at the end of the sixth week.

Figure 1. Animal grouping and experimental design. A. The mice were allocated into 3 groups of 5 animals: control, ethanol and ethanol+ cerulein. B. Schematic representation of the experimental design and timing of the injections duringsix weeks of experimental period.

Blood collection

At the end of the sixth week all mice were anesthetized using a combination of Ketamine (100mg/kg) and xylazine (10mg/kg). The animals were sacrificed by exsanguination through the cardiac puncture and sacrificed by neck dislocation.

Biochemical assays

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), amylase and lipase (U/l), Gamma GT (U/l) were determined using commercial kits.

Isolation of pancreatic acinar cells

Acini were isolated with minor modifications to the standard procedure. The pancreas was excised and placed into 6 mL of acinar media, containing (inm M):40Tris(pH7.4),95NaCl, 4.7KCl,0.6MgCl2,1.3MgCl2,1NaH2PO4,10glucose,2 glutamine, 0.1% BSA, and 1X MEM amino acids, with 50 units/mL of collagenase type 5 (Sigma-Aldrich). The pancreas was insufflated for 5 minutes with the collagenase media, then minced and placed into a 50 mL flask containing 12 mL of collagenase media. The mixture was incubated at 37°C with shaking (120 rpm) for 60 minutes. After incubation, the digest was filtered through a 300-400 µm mesh.

Measurement of fluid phase endocytosis

For uptake of Texas Red dextran-10, acinar cells were incubated with this fluorescence labelled marker at 37 °C for 2 hours and then monitored under a phase contrast microscope with fluorescence attachment (DeWinter Technologies) at 200X magnification.

Pancreas tissue preparation and haematoxylene-eosin staining

Immediately after scarifice the pancreas tissues were removed. One part was fixed in 10% buffered formalin for 24 hours, routinely processed, and embedded in paraffin. Serial paraffin sections of 4 µm thickness were prepared, stained with haematoxylin and eosin (H&E) and used for histopathological analysis.

Statistical analysis

All statistical parameters were analyzed using GraphPad Prism (Version 9.0) statistical software. Data were presented as Mean± SEM. Data were checked for normality by Shapiro-Wilk test and one way ANOVA was performed followed by Tukey's multiple comparison test. Differences were considered significant if $P<0.05$.

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Results

Disrupted amylase activity in an ethanol-cerulein induced mouse model of chronic pancreatitis

Amylase activity is a key biomarker in diagnosing pancreatitis, as the enzyme is primarily produced by the pancreas to aid in carbohydrate digestion. During acute pancreatitis, inflammation causes excessive release of amylase into the bloodstream, leading to elevated serum amylase levels. Measuring amylase levels helps in early detection and monitoring of pancreatic disorders. In our study, a significant increase in amylase activity was observed in the group of animals administered with ethanol + cerulein compared to the control group ($p < 0.0001$) and the group received only ethanol($p<0.001$) (Figure2A). In contrast, the group that received only ethanol exhibited a relatively lower but still elevated amylase activity. These findings suggest that the combined administration of ethanol and cerulein induces a more pronounced pancreatic response, likely exacerbating pancreatic stress and dysfunction.

Altered lipase activity in a mouse model of chronic pancreatitis induced by ethanol and cerulein

Lipase is a crucial digestive enzyme produced by the pancreas that helps break down fats into fatty acids and glycerol. In pancreatitis, inflammation of the pancreas leads to excessive release of lipase into the bloodstream, making elevated serum lipase levels a key diagnostic marker for the condition. Persistent high lipase activity can indicate severe pancreatic damage, leading to complications such as tissue necrosis and systemic inflammation. There was no statistically significant change in lipase activity in the group that received ethanol alone. However, a notable and significant increase in lipase activity was observed in the group that was administered both cerulein and ethanol as compared to control group ($p < 0.05$) and the group received only ethanol ($p <0.05$) (Figure2B). This suggests that while ethanol alone does not substantially impact pancreatic lipase levels, its combination with cerulein exacerbates pancreatic enzyme secretion, likely contributing to pancreatic inflammation and dysfunction.

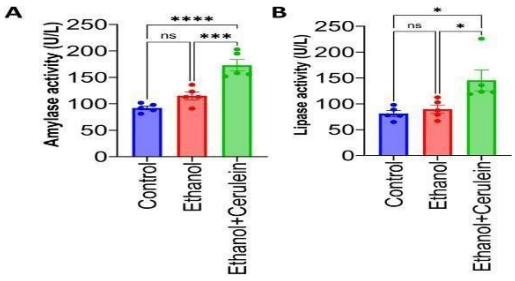

Figure 2: Changes in A. Amylase activity and B. Lipase activity in a mouse model of chronic pancreatitis induced by ethanol and cerulein.

Data were presented as Mean±SEM (n = 5). Normality of data was tested by Shapiro–Wilk test. Significance level based on one-way ANOVA, $p < 0.05$. Significance level based on Tukey' sposthoctest*$p<0.05$,**$p<0.01$,***$p<0.001$, ****$p<0.0001$,ns-notsignificant.

Dysregulated AST and ALT levels in an ethanol-cerulein induced mouse model of chronic pancreatitis

AST(SGOT)and ALT(SGPT)are liver enzymes that can also indicate pancreatic damage, especially in acute pancreatitis. Elevated AST and ALT levels in pancreatitis suggest inflammatory stress, tissue injury, or biliary involvement. A significant increase, particularly in ALT, may indicate gallstone-induced pancreatitis, as bile duct obstruction affects both the liver and pancreas. Their levels help in differentiating between alcoholic and gallstone-related pancreatitis and assessing severity. Monitoring these enzymes is crucial for early diagnosis, prognosis, and guiding treatment strategies in pancreatic disorders. In this study, a significant elevation in AST levels was observed in both experimental groups—one receiving ethanol administration ($p < 0.05$) and the other receiving a combination of ethanol and cerulein ($p < 0.0001$) (Figure 3A) when compared to the control group. Similarly, ALT levels were also significantly increased in both groups, with the ethanol-treated group showing a notable rise in the ethanol+cerulein administered group exhibiting a comparable elevation ($p < 0.01$) (Figure3B).

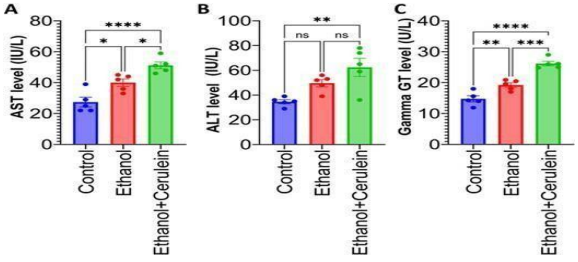

Figure 3: Alterations in A. AST Level (IU/L), B. ALT Level (IU/L), and C. Gamma GT (U/L) levels in the ethanol-cerulein induced mouse model of chronic pancreatitis. Data were presented as Mean±SEM (n = 5). Normality of data was tested by Shapiro–Wilk test. Significance level based on one-way ANOVA, $p < 0.05$. Significance level based on Tukey'spost hoc test *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns-not significant.

Impaired Gamma-GT activity in an ethanol-cerulein induced model of chronic pancreatitis

Gamma-glutamyl transferase (GGT) is an enzyme involved in amino acid transport and glutathione metabolism, commonly used as a marker for liver and biliary diseases. Elevated GGT levels are often observed in pancreatitis, particularly in cases related to alcohol-induced pancreatic injury, as chronic alcohol consumption leads to oxidative stress and inflammation in both the liver and pancreas. GGT serves as an indirect marker of pancreatic dysfunction, reflecting biliary obstruction, oxidative stress, and systemic inflammation, all of which are relevant in pancreatitis. In this study the gamma GT activity was found significant in the group that has been administered with ethanol as compared to control as well as the group that has been administered with ethanol+cerulein ($p<0.0001$) as compared to both the control group and the ethanol administered group ($p<0.001$) (Figure 3C).

Effect of ethanol and cerulein on Texus Red-Dextran uptake in pancreatic acinar cells in a mice model of chronic pancreatitis

Texus Red-dextran was employed as a fluorescent marker to assess fluid-phase endocytosis. Inethanol+cerulein-treated cells, a significant increase was observed not only in the number but also in the size of Texas Red-Dextran-labelled structures when compared to control and ethanol-only treated cells. This

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Suggests enhanced endocytic activity and vesicular trafficking in response to the combined ethanol and cerulein treatment. These findings highlight the impact of ethanol and cerulein co-treatment on cellular dynamics, potentially contributing to the pathological changes observed in the experimental model.

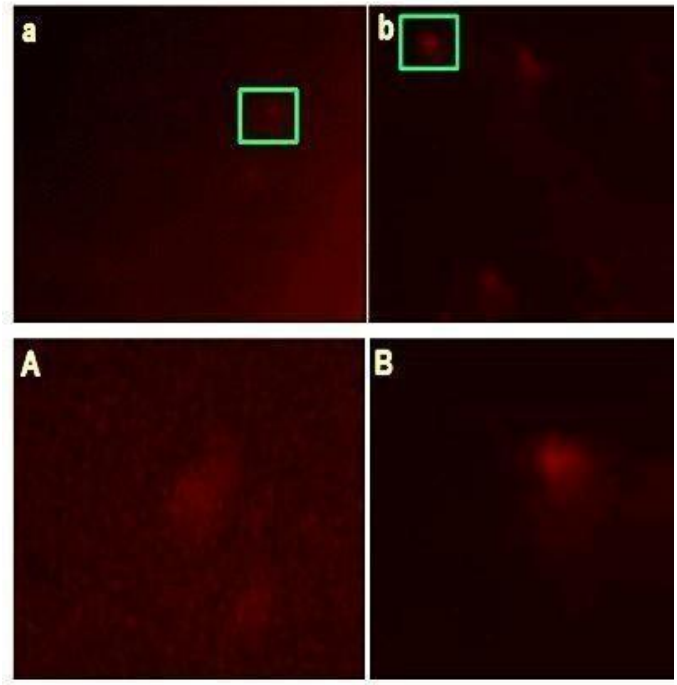

Figure 4: Texas Red-Dextran uptake - a fluid phase endocytosis marker in acinar cells of control (a & A), ethanol treated (b&B) and ethanol+cerulein(c&C) treated mice in a chronic pancreatitis model.

Histopathological evaluation

Light microscopic examination of haematoxylin-eosin-stained sections revealed no perceptible signs of chronic pancreatitis development in mice treated with ethanol only but without caerulein treatment. In contrast, mice given both ethanol and cerulein revealed the presence of acinar loss including glandular atrophy, enlarged interstitial spaces and degeneration. All these results pointing to the successful and more robust induction of chronic pancreatitis by adding ethanol to cerulein treatment.

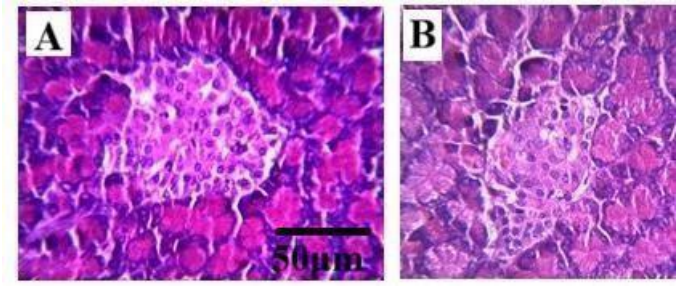

Figure 5: Haematoxylene-eosin stained sections of pancreas of mice (Magnification: 400X, Scale bar: 50µm). A. Control: normal architecture of pancreas. B. Ethanol treated: No perceptible sign of chronic pancreatitis development. C: Ethanol+Cerulein treated: notable alterations include glandular atrophy, enlarged interstitial spaces, epithelial cell degeneration, and necrosis.

Discussion

The findings of this study align with previous research indicating that chronic alcohol consumption increases susceptibility to pancreatitis when exposed to low doses of CCK analogues, which do not typically induce pancreatitis in control-fed animals. Notably, our results highlight that the impact of ethanol on the pancreas is closely linked to endogenous cholinergic pathways. When combined with earlier reports, these findings suggest that in alcohol-fed animals, CCK-induced cholinergic activation triggers pathophysiological responses associated with pancreatitis. This underscores the critical role of the endogenous cholinergic system, which, when activated by submaximal doses of CCK or other stimuli, can independently drive pancreatitis in alcohol-exposed animals. These in sights are particularly relevant, as they challenge the conventional approach of using supraphysiological doses of exogenous CCK analogues, such as cerulein, in experimental models, which may not fully mimic the disease's initiation in humans.

Dietary intake could play a significant role in this process, as studies have reported that individuals with alcohol-induced pancreatitis tend to consume higher amounts of fat and protein (Ul Ain et al., 2021). This dietary pattern is expected to elevate intestinal CCK secretion, thereby enhancing cholinergic stimulation (Wang et al., 2019). We propose that the combined effects of chronic alcohol exposure, increased nutrient load, and CCK release, along with acinar cell sensitization, transform normal physiological responses into pathological ones.

Amylase and lipase are well-established biomarkers of pancreatitis, providing valuable diagnostic and prognostic insights. Our study observed a significant elevation in serum amylase and lipase levels in ethanol- and cerulein-treated animals, with the highest increase in the combined treatment group. These findings confirm pancreatic tissue injury following exposure to both ethanol and cerulein.

Chronic alcohol consumption is a major risk factor for both chronic pancreatitis (CP) and liver cirrhosis (LC), with disease severity correlating strongly with the amount of alcohol consumed. Given the shared aetiology, CP and LC frequently co-exist in affected individuals. Understanding their co-occurrence and associated risk factors may offer deeper insights into their underlying mechanisms (Aparisi et al., 2008). To evaluate liver function, we measured serum levels of AST and ALT, which are key indicators of hepatic health. Ethanol- and cerulein-treated mice showed elevated levels of both enzymes compared to controls, indicating liver damage. Additionally, gamma-glutamyl transferase (GGT), a sensitive marker of hepatobiliary dysfunction, was significantly increased in ethanol- and cerulein-exposed animals. The concurrent rise in AST, ALT, and GGT suggests substantial hepatic impairment, emphasizing the interconnection between chronic pancreatitis and liver dysfunction (Liu et al.,2021). These findings highlight the importance of monitoring liver enzyme profiles in pancreatitis patients, especially those with alcohol-related liver disease.

For the past two decades, the prevailing hypothesis has suggested that a critical early cellular event in pancreatitis is the formation of large cytoplasmic vacuoles, where lysosomal enzymes and zymogens become co-localized (Perez et al.,2015). This co-localization results in the premature activation of zymogens, ultimately leading to intracellular digestion and cellular damage. Normally, acinar cells release zymogens, which

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are transported through the pancreatic duct system into the duodenum, where their activation occurs under physiological conditions (Saluja et al., 2019). This transport process is dependent on fluid secretion from both pancreatic acinar and ductal cells. However, in pathological conditions such as pancreatitis, disruptions in this process can lead to zymogen activation within the pancreas rather than the intestine (Hegyi et al., 2011).

Our study found a significant accumulation of Texas Red dextran-10, a fluid-phase endocytosis marker, in animals co-administered ethanol and cerulein. This observation suggests that some zymogens undergo activation within the pancreatic tissue itself, rather than following their normal pathway to the intestine. Such premature activation is likely a key trigger for pancreatic autodigestion, contributing to the development and progression of pancreatitis (Manohar et al., 2017). These findings provide further insights into the cellular mechanisms underlying the disease, highlighting the role of disrupted zymogen transport and activation.

The findings of this study establish that repeated cerulein injections in combination with ethanol exposure successfully induce a mouse model of chronic pancreatitis, accompanied by concurrent pancreatic and hepatic dysfunction. The significant elevation of serum biomarkers, including amylase and lipase for pancreatic function and AST, ALT, and gamma-GT for hepatic function, underscores the impact of this model on both organs. Additionally, the increased accumulation of fluid-phase endocytic markers in acinar cells suggests that alterations in endocytic vesicle dynamics may represent an early pathological event in chronic pancreatitis. These insights contribute to a deeper understanding of the mechanisms underlying alcohol-induced chronic pancreatitis, potentially aiding in the development of targeted therapeutic strategies for this debilitating disease.

In conclusion, the findings indicate that the combined ethanol and cerulein treatment produced significant biochemical and histopathological alterations—including acinar loss and glandular atrophy—not seen with ethanol alone. Enhanced fluid-phase endocytosis, shown by increased Texus Red-Dextran uptake, underscores disrupted cellular processes contributing to pancreatic damage. These synergistic effects advance our understanding of the mechanisms underlying pancreatic injury.

Declarations:

Competing interests

All the authors declare that there are no conflicts of interest.

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Noexternalfundingwasreceivedforthisstudy.

Data availability

The data supporting this study's findings can be obtained from the corresponding author upon reasonable request.

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