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Promoting effect of adipocytokine, apelin, on hepatic injury in caerulein-induced acute pancreatitis in rats
Apelin on AP-induced hepatic injury

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Abstract *Objective:* To evaluate the potential apelin effect on hepatic injury in caerulein (Cn) -induced AP in rats.

Experimental protocol: Thirty male albino rats were divided into three groups, 10 rats each: control group: received 0.9% NaCl solution. AP group: received (Cn, 50 μg/kg/h, i.p.) for 6 h. Apelin-13 treated AP group: received apelin 13, 50 nmol/kg/h, i.p, immediately after each Cn injection, starting after the second Cn dose. 12 h after the last Cn injection, the rats were sacrificed, and serum amylase, lipase, phospholipase A2 (PLA2), interleukin (IL)-6, IL-1β, IL-10, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactic dehydrogenase activity (LDH) were assayed. The hepatic malondialdehyde (MDA), reduced glutathione (GSH) and catalase (CAT) levels, caspase-3 activity and tumor necrosis factor-alpha (TNF-α) were assessed, while myeloperoxidase (MPO) was determined in pancreatic and hepatic tissues.

Results: Cn injection caused severe AP, with marked hepatic damage. The exogenous apelin reduced Cn-induced pancreatic and hepatic injury with reduction in hepatic oxidative, apoptotic and inflammatory markers, pancreatic and hepatic MPO activity with modulation of inflammatory cytokines.

Conclusion: Apelin could be protective in AP associated liver damage, possibly through antioxidant, anti-apoptotic mechanisms with modulating the inflammatory mediators.

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1. Introduction

AP is a non-infectious inflammatory disease, associated with autodigestion of the pancreas, with sudden onset and rapid progression.[1]

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Clinically ranges from a mild, self-limiting localized disease to severe AP often lead to distant organ dysfunction and high mortality.[2]

AP induced liver injury is considered to be an important prognostic indicator in AP, and may develop into hepatic failure and even result in death. Thus, it is of importance to protect liver function and block injury-related pathways.[3]

The pathophysiology of AP and its associated liver injury are heterogeneous and involve a complex cascade of events.[4] Recent studies have shown that inflammatory cytokines, and adhesion molecules such as TNF-α, IL-6, and IL-1β produced within the pancreas and systemically, as well as neutrophil activation and adhesion contribute to the development and severity of AP and its complicated organs dysfunction.[5]

Both necrosis and apoptosis occur in experimental pancreatitis. It is now well known that the severity of the disease is related to the type and the degree of cell death induced by different etiologic factors.[6]

Several experimental[7] and clinical studies,[8] have provided some support for the concept that oxidative stress is the common pathway for the pathogenesis of AP and associated hepatic injury.

Current Cn induced AP model reproduces the cardinal features of human pancreatitis including elevated serum amylase/lipase and pancreatitis-associated complications. Cn induces secretory block which is followed by lysosomal degradation of intercellular organelles within autophagic vacuoles in acinar cells, a marked interstitial edema and premature intracellular protease activation.[9]

Apelin, a small regulatory peptide, has been identified as the endogenous ligand of the human orphan G protein-coupled receptor APJ, a receptor structurally related to the angiotensin II (ANG II) receptor AT_1. It can act via autocrine, paracrine, endocrine, and exocrine signaling.[10]

Apelin is synthesized as a 77 amino acid prepropeptide that is cleaved into several active isoforms, with apelin-13 is the final active product, being the most potent isoform, more resistant to enzymatic cleavage, with a brief plasma half-life in man and relatively short lived effects.[11]

The apelin-APJ axis is widely expressed in heart, brain, lung, kidney as well as the gastrointestinal tract, on pancreatic duct, acinar and islets cells and hepatic parenchymal, Kupffer (KCs), stellate and endothelial cells.[12]

Apelin peptides have been shown to affect many biological functions in mammals including the neuroendocrine and immune systems.[10] Apelin signaling is known to play important roles in cardiovascular homeostasis; however, its functions in liver injury associated with AP remain unclear.[13]

Hans et al. proved upregulated pancreatic apelin expression during Cn-induced AP in mice.[14]

Multiple therapeutic modalities have been suggested for AP and its related organ dysfunction, which remain largely supportive but none has been unambiguously proven to be effective yet[2]

The aim of this study was to assess the role of apelin-signaling in the pathophysiology of the AP induced liver injury, and evaluate potential new therapeutic strategies through highlighting the effect of exogenous apelin-13 on liver injury in a rat model of Cn-induced AP and the mechanisms behind apelin's effect.

2. Material and methods

2.1. Animals and experimental design

This study was carried out on thirty male albino rats weighing about 200–250 g. The rats were housed, four per cage, under standard laboratory conditions at room temperature (24 ± 2 °C), and had free access to water and food. The rats were fasted during the night before the experiment. All animal experiments were undertaken with the approval of Ethical Animal Research Committee of Tanta University.

The rats were randomly divided into three groups (10 rats each):

2.2. Control group

The rats were given hourly, i.p injection of 2 ml 0.9% NaCl saline solution, throughout the experimental period.

2.3. Acute pancreatitis (AP) group

AP was induced by i.p. injection of a supra-maximal concentration of (Cn) (50 μg/kg), (Sigma–Aldrich Chemical, Steinheim, Germany), diluted in 2 mL saline, every hour for a total of 6 h. At the end of Cn injections, the rats were given 2 mL i.p. saline till the end of experiment.[15]

Cn is a stable cholecystokinin analogue, leading to proteolytic enzyme secretion that causes pancreatic acinar autolysis with progressive interstitial edema just one hour after injection. It is used to induce experimental AP models in rats and mice.[9]

2.4. Apelin-13 treated acute pancreatitis group

Apelin-13 (Apelin®, Phoenix Pharmaceutical, Belmont, CA, USA), is given (50 nmol/kg/h, i.p.),[16] dissolved in 2 ml saline, immediately after each Cn injection starting after the second Cn dose.

At the end of experiment, 12 h after the last Cn injection, the rats were sacrificed and blood samples were collected, immediately centrifuged at 3000*g* for 10 min, and the supernatant was stored at −20 °C for biochemical assays. Tissue samples of pancreas and liver of all groups were quickly removed and kept frozen at −80 °C for further analysis. Hepatic and pancreatic protein content was determined according to the method of Lowry et al.[17]

The following parameters were determined.

2.5. Liver function assay

Serum (ALT) and (AST), as indicators of liver functions, were measured according to the method of Rei.[18]

Serum (LDH) activity, as a marker of tissue injury, was assayed according to the method of Martinek.[19]

2.6. Liver caspase-3 activity and (TNF-α) assay

Liver caspase-3, the common signal molecule of various apoptotic mechanisms and TNF-α, was measured by the enzyme-

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