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TOPIC HIGHLIGHT

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Acute pancreatitis: The stress factor

Marcelo G Binker, Laura I Cosen-Binker

Marcelo G Binker, Laura I Cosen-Binker, CBRHC Research Center, 1053 Ciudad Autónoma de Buenos Aires, Buenos Aires 1426, Argentina
Laura I Cosen-Binker, Department of Molecular and Cell Biology, Henry M Goldman School of Dental Medicine, Boston University, Boston, MA 02118, United States
Author contributions: Binker MG and Cosen-Binker LI contributed equally to this work.
Supported by KB and Associates Representing Certification International (United Kingdom) Limited
Correspondence to: Dr. Laura I Cosen-Binker, Department of Molecular and Cell Biology, Henry M Goldman School of Dental Medicine, Boston University, 72 East Concord Street - Evans Building - Room 408, Boston, MA 02118, United States. licb@bu.edu
Telephone: +1-617-4141084 Fax: +1-617-4141041
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Abstract

Acute pancreatitis is an inflammatory disorder of the pancreas that may cause life-threatening complications. Etiologies of pancreatitis vary, with gallstones accounting for the majority of all cases, followed by alcohol. Other causes of pancreatitis include trauma, ischemia, mechanical obstruction, infections, autoimmune, hereditary, and drugs. The main events occurring in the pancreatic acinar cell that initiate and propagate acute pancreatitis include inhibition of secretion, intracellular activation of proteases, and generation of inflammatory mediators. Small cytokines known as chemokines are released from damaged pancreatic cells and attract inflammatory cells, whose systemic action ultimately determined the severity of the disease. Indeed, severe forms of pancreatitis may result in systemic inflammatory response syndrome and multiorgan dysfunction syndrome, characterized by a progressive physiologic failure of several interdependent organ systems. Stress occurs when homeostasis is threatened, and stressors can include physical or mental forces, or combinations of both. Depending on the timing and duration, stress can result in beneficial or harmful consequences. While it is well established that a previous acute-short-term stress decreases the severity of experimentally-induced pancreatitis, the worsening effects of chronic stress on the exocrine pancreas have received relatively little attention. This review will focus on the influence of both prior acute-short-term and chronic stress in acute pancreatitis.

Key words: Pancreatitis; Acute stress; Chronic stress; Heat shock proteins; Tumor necrosis factor alpha

Core tip: Depending on the timing and duration, stress can result in beneficial or harmful consequences. Regarding the exocrine pancreas, a previous acute-short-term stress decreases the severity of experimentally-induced pancreatitis. This protection is conferred by distinct heat shock proteins (HSP) including HSP27, HSP60 and HSP70. Conversely, chronic stress increases the susceptibility of the exocrine pancreas, aggravating pancreatitis episodes. These worsening effects are mainly mediated by tumor necrosis factor alpha.

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INTRODUCTION

Acute pancreatitis is an inflammatory disorder of the pancreas with an overall mortality of approximately 5%[1]. Etiologies of pancreatitis vary, with gallstones accounting for the majority of all cases, followed by alcohol. Other causes of pancreatitis include trauma, isch-

emia, mechanical obstruction, infections, autoimmune, hereditary, and drugs[2].

The main events occurring in the pancreatic acinar cell that initiate and propagate acute pancreatitis include inhibition of secretion, intracellular activation of proteases, and generation of inflammatory mediators[3]. These cellular events can be correlated with the acinar morphological changes (retention of enzyme content, formation of large vacuoles containing both digestive enzymes and lysosomal hydrolases, and necrosis), which are observed in the well-established *in vivo* experimental model of supraphysiological cerulein-induced pancreatitis[4], as well as in human acute pancreatitis[5]. Chemokines released from damaged pancreatic cells attract inflammatory cells, whose systemic action ultimately determined the severity of the disease. Indeed, severe forms of pancreatitis may result in systemic inflammatory response syndrome and multiorgan dysfunction syndrome, characterized by a progressive physiologic failure of several interdependent organ systems[6].

Stress can be defined as "threatened homeostasis", and stressors can include physical or mental forces, or combinations of both. The reaction of an individual to a given stressor involves the stimulation of pathways within the brain leading to activation of the hypothalamic-pituitary-adrenal axis and the central sympathetic outflow[7]. This can result in visceral hypersensitivity through the release of different substances, such as substance P and calcitonin gene-related peptide from afferent nerve fibers[8].

The main source of pancreatic innervation comes from both vagus nerves and the celiac ganglion complex. The cephalic segment is innervated by the right celiac complex and the hepatic and mesenteric plexus coming from the right vagus. The splenic segment is innervated by the left celiac nerve and the splanchnic nervous network. Except for the gastro-duodenal branches network, most of the nerves enter the gland by its periphery and concentrate in the cephalic segment, which exhibits an important number of ganglion cells. These characteristics of the macroscopic innervation decrease in a significant and progressive fashion towards the splenic segment[9,10].

While it is well established that a previous acute-short-term stress decreases the severity of experimentally-induced pancreatitis[11-17], the worsening effects of chronic stress on the exocrine pancreas have received relatively little attention[18-20]. This review will focus on the influence of both prior-acute-short-term and chronic stress in acute pancreatitis.

ACUTE STRESS

Preceding acute-short-term stress is a well-known inductor of cellular protection against numerous pathological conditions, including renal ischaemia, heart ischaemia, brain ischaemia, enterocolitis and pancreatitis[11-17,21-25]. Exposure of organisms to an initial sublethal stress leads to the synthesis of heat shock proteins (HSP) and confers protection against further stress[26]. HSP comprise a highly conserved family of proteins with molecular sizes ranging from 10 to 110 kDa. These molecular chaperones are involved in synthesis, folding, transport and degradation of proteins, and can be induced by stressful conditions such as infection, inflammation, hypoxia, starvation, heat shock, water immersion, and oxidative stress[27-29].

The eventual protection conferred by acute stress-induced HSP in pancreatitis, seems to be stressor- and disease-inducer-dependent[30,31]. Water immersion and heat shock induce pancreatic HSP60 and HSP70, respectively, and protect rats from cerulein-induced acute pancreatitis by inhibiting autophagy, which prevents the subcellular redistribution of cathepsin B and the activation of trypsinogen[14,32,33]. Additionally, hyperthermia- or chemical-stimulated HSP70 also decrease the production of inflammatory mediators by downregulation of NF-κB[34,35]. Remarkably, transgenic mice knock-out for HSP70 (*HSP70.1*$^{-/-}$) develop spontaneous activation of pancreatic trypsinogen[36]. However, transgenic knock-in mice over-expressing HSP72 do not exhibit protection for development of cerulein-induced acute pancreatitis, but HSP72 over-expression accelerates tissue injury recovery by lessening NF-κB signaling[37]. Heat shock also induces pancreatic protection against cerulein hyperstimulation by upregulating HSP27[38]. Indeed, over-expression of HSP27 preserves the actin cytoskeleton of pancreatic acinar cells and protect against cerulein-induced pancreatitis in a specific phosphorylation-dependent manner[39]. HSP27 exerts a similar protective effect in coronary arteries[40]. Vessels (endothelial and/or smooth muscle cells) from patients with ischemic heart disease exhibit decreased levels of HSP27 (in particular phospho-HSP27), which correlates with destabilization of the actin cytoskeleton[40]. Regardless of the underlying mechanism, disorganization of the actin cytoskeleton is associated with dysregulation of pancreatic enzyme secretion[41]. Interestingly, HSP27 seems to coordinate activity with other HSP members to provide the full extent of resistance to injury[42]. For instance, , depletion of HSP70 in renal cells does not impede association of HSP27 with actin, but prevents maximal cytoprotective effect against energy depletion[42].

Other pancreatitis-induced models exhibit some differences with the previously mentioned, secretagogue hyperstimulation. Thus, hyperthermia protects against subsequent L-arginine-induced acute pancreatitis in rats by increasing pancreatic expression of HSP70 and HPS27, and phosphorylation of HSP27, but without changing HSP60 levels[15,43]. As observed in the cerulein model, transgenic mice over-expressing HSP72 do not exhibit protection for L-arginine-induced acute pancreatitis[37]. However, HSP72 over-expression does not accelerate tissue injury recovery in L-arginine treated animals[37]. Although both hot and cold water immersion induce pancreatic HSP72 and HSP60, respectively, only cold water

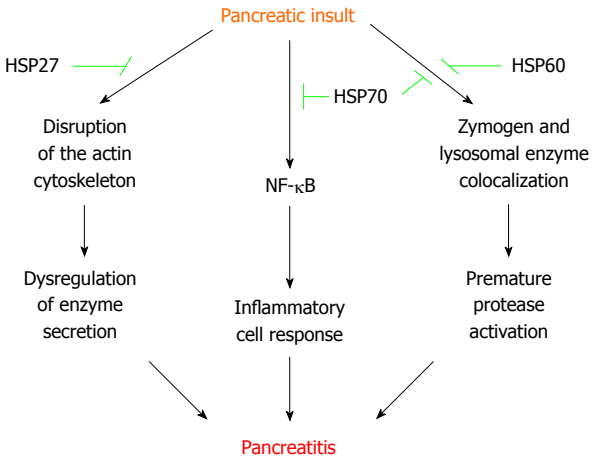

Figure 1 Hypothetical mechanisms underlying prior-acute-short-stress protects against pancreatitis. Pancreatic insults may provoke dysregulation of enzyme secretion, premature protease activation and inflammatory acinar response, which result in the development of pancreatitis. Different stressors such as hyperthermia, hypothermia, hypoxia, energy depletion and chemicals, can induce pancreatic heat shock proteins (HSP) by a prior-acute-short-stress exposition. Distinct HSP avoid the disruption of the actin cytoskeleton, zymogen/lysosomal enzyme colocalization and activation of the pro-inflammatory nuclear factor-kappa beta (NF-κB) caused by the pancreatic insult. These HSP-mediated effects seem responsible for the protection against pancreatitis. The specific pathway inhibited by each HSP is depicted in green.

immersion slightly protect rats from sodium tauracholate-induced acute pancreatitis, pointing the transcendence of the subcellular redistribution of cathepsin B in this necrohemorrhagic pancreatitis model[13].

Nevertheless, prior-acute-short-term stress protects against pancreatitis by distinct HSP, which seem to exert its beneficial effects through different pathways (Figure 1).

CHRONIC STRESS

Chronic stress has been proved to increase the susceptibility of different rat organs, such as the small intestine, colon and brain, to inflammatory diseases[8,20,44-46], as well as to aggravate atherosclerotic lesions in mice[47].

Even though oxidative stress and inflammation each occur in the pancreas during the early stage of supramaximal cerulein-induced acute pancreatitis model, neither oxidative stress nor an inflammatory insult alone cause the characteristic changes of acute pancreatitis[48]. However, chronic stress leaves the exocrine pancreas susceptible to pancreatitis by submaximal cerulein stimulation[20]. Pancreatic tissue from rats chronically exposed to restraint exhibit measurable levels of the pro-inflammatory cytokine tumor necrosis factor α (TNF-α) as well as a low but detectable leukocyte infiltrate and myeloperoxidase activity[20], suggesting leukocytes as a feasible source of TNF-α induced by chronic stress. Interestingly, *in vitro* incubation of mice pancreatic acini with phorbol-12-myristate-13-acetate-activated neutrophils or macrophages directly induce intracellular trypsinogen activation and cell death, being protease activation and necrosis mediated by leukocyte-secreted TNF-α in a cathepsin-B and calcium-dependent manner[49].

TNF-α has an important role in various biological functions, including cell proliferation, cell differentiation, survival, apoptosis and necrosis[50], and in stress-related inflammatory disorders[45-47,51]. For a long time, it has been known that TNF-α participates in the inflammatory cascade which propagates pancreatitis[52]. Nevertheless, its relevance in the genesis of this debilitating disease only recently captured the attention of research investigation[20,49].

Secretion of TNF-α by several stress stimuli has been demonstrated *in vitro* in many cell types, including pancreatic acinar cells[53-60], and *in vivo* in different tissues[47,51,61-63]. Our lab has shown that *in vitro* hypoxia-reoxygenation conditions also induce TNF-α secretion by acinar cells[20]. These conditions are concomitant with ischemia-reperfusion processes, which can be the result of microcirculatory disturbances generated by stress[64]. Indeed, local pancreatic blood flow is reduced by stress[65]. Hence, alternate vasoconstriction and vasodilatation leading to tissue ischemia and reperfusion could reflect another putative local origin of chronic stress-derived TNF-α found in the pancreatic tissue. This is supported by the increased levels of the transcription factor hypoxia inducible factor 1 alpha (HIF-1α) observed in experimentally stressed rats[20]. HIF-1α is induced by hypoxic conditions and is involved in different inflammatory processes, such as dermatitis, rheumatoid arthritis[66], and also pancreatitis[67].

Different reports evaluated the response of pancreatic acinar cells to exogenous TNF-α, showing disruption of the typical filamentous actin distribution[20,68]. A similar redistribution of actin from apical to basolateral membranes was observed in pancreatic acini supra-stimulated with CCK[69]. While TNF-α alone does not stimulate amylase secretion in human pancreas[70] or in isolated rat pancreatic acini[20,68], it certainly inhibits submaximal CCK-stimulated amylase secretion[20]. Although necessary, the inhibition of pancreatic enzyme secretion alone is not sufficient to induce pancreatitis[3]. Nonetheless, TNF-α also activates pancreatic acinar nuclear factor-κB (NF-κB), a key transcriptional regulator of the expression of inflammatory molecules[20,68,71,72]. Consistently, rat pancreatic acinar cells treated with high doses of exogenous TNF-α, exhibit a notable increase in the production of cytokines interleukin (IL)-1β, IL-4, IL-6, IL-10, as well as TNF-α[73].

TNF-α has been shown to regulate the activity of distinct protein kinase C (PKC) isoforms in diverse cell types, including the pancreatic acinar cell[72,74,75]. PKC family comprises at least 12 members differing in tissue distribution and activation requirements. There are three subclasses: classical PKC isozymes (-α, -β1, -β2, and -γ), which require calcium and are activated by diacylglycerol and phorbol ester; the novel PKC isozymes (-δ, -ε, -η, and -θ), which are activated by diacylglycerol and phor-

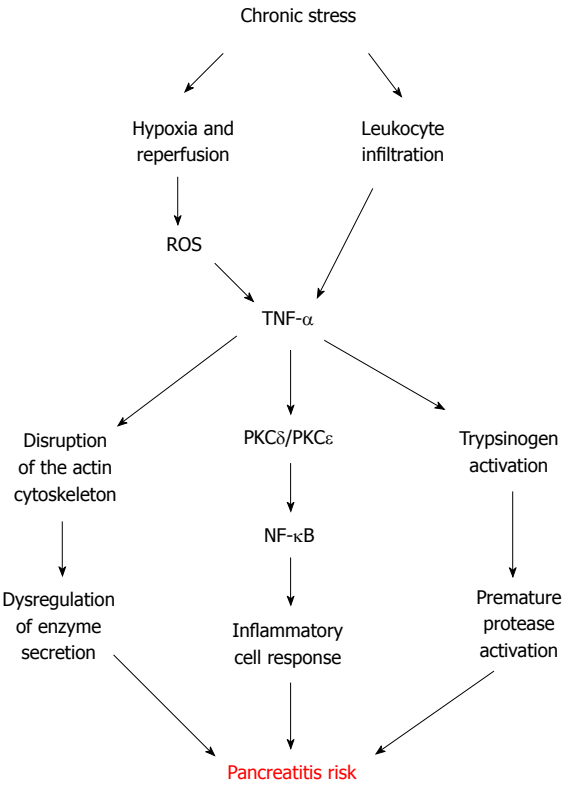

Figure 2 Hypothetical mechanisms involved in chronic stress sensitizes to pancreatitis. Chronic stress compromises the exocrine pancreas by generating ischaemia and reperfusion processes, as well as attracting leukocytes to the pancreatic parenchyma. Ischaemia and reperfusion induce hypoxia and reoxygenation conditions that generate the intrapancreatic reactive oxygen species (ROS) responsible for acinar tumor necrosis factor-alpha (TNF-α) production. TNF-α released from both pancreatic acinar cells and leukocyte infiltrate, impact on pancreatic acinar cells producing disruption of the actin cytoskeleton (redistribution from apical to basolateral membrane), a protein kinase C delta (PKCδ)- and PKC epsilon (PKCε)-mediated activation of the transcription factor nuclear factor-kappa beta (NF-κB), and an increase in levels of active trypsin. Dysregulation of enzyme secretion, induction of inflammatory acinar response and premature intra-acinar protease activation associated to these pathological pathways sensitize the exocrine pancreas to pancreatic insults and increase the risk to develop pancreatitis.

bol ester independently of calcium; and the atypical PKC isozymes (-λ, -ι, and -ζ), which are calcium independent and not responsive to phorbol ester. Rat pancreatic acini express the α, δ, ε, and ζ PKC isozymes[76]. Changes in PKC activity are associated with inflammation in a variety of tissues, including skin, kidney, intestine, and pancreas[77-80]. Specifically, PKC-δ and PKC-ε regulate the signal transduction pathways implicated in the pathophysiological activation of NF-κB and trypsinogen in rat pancreatic acini[72,81]. TNF-α activates both PKC-δ and PKC-ε in rat pancreatic acini[72], which convert physiological CCK concentrations into phytopathogenic concentrations[20]. Different studies have consistently shown that modulation of PKC activity sensitizes acinar cells to physiological secretagogue treatments, resulting in harmful levels of NF-κB and trypsin activity[81,82]. In agreement, TNF-α plus submaximal CCK pathologically activates NF-κB and trypsinogen in rat pancreatic acini, and induced both apoptosis and necrosis[20]. However, pancreatic acini response from rats seems to differ from that observed in mice, since TNF-α by itself only induces trypsinogen activation and necrosis in mice, with an extent comparable to supramaximal cerulein stimulation[20,49]. This could be a concentration-dependent effect or relative to differences between species, which is well-documented for experimentally-induced pancreatitis in rodents[83-86], but further studies are required to address this disparity in pancreatic acinar response to exogenous TNF-α.

Summarizing this topic, chronic stress appears as a risk factor to develop pancreatitis by sensitizing the exocrine pancreas through TNF-α, which seems to exert its detrimental effects through different pathways (Figure 2).

CONCLUSION

Depending on the timing and duration, stress can result in beneficial or harmful consequences for the exocrine pancreas. Prior acute-short-term stress could be useful for high-risk procedures such as endoscopic retrograde cholangiopancreatography. Conversely, the management of chronic stress appears critical for patients with risk of pancreatitis. Nonetheless, the mechanisms underlying protection by previous-acute-short-term stress as well as burden by chronic stress, have to be further explored.

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