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Cerulein induced acute pancreatitis through activation of oxidation stress and inflammation

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Abstract
Cerulein induced acute pancreatitis, is the widely used experimental model for the induction of AP as it is economical with high reproducibility. Cerulein being a cholecystokinin (CCK) analogue, aids in the secretion of digestive enzymes thereby hyperstimulation of the exocrine pancreas with high cerulein dose stimulates the pancreas resulting in the upregulation of the inflammatory mechanisms through activation of NFκB and release of Reactive Oxygen species (ROS) which go hand in hand that lead to acute pancreatitis condition.

Keywords: Acute pancreatitis (AP), Cerulein, oxidative stress, inflammation

1. Introduction
Cerulein was discovered in the Australian green tree frog (*Litoria caerulea*) by Italian and Australian researchers in late 90's and is known to be used for inducing both acute and chronic pancreatitis with high success rate. At first, Lampel and Kern (1977) [13] described a model of acute edematous pancreatitis produced by hyperstimulation of the exocrine pancreas with cerulein. Mouret (1895) [17] reported that the pathological changes induced in the pancreas could be attributed to excess stimulation of cholinergic nervous system. Cerulein-induced AP is the widely used experimental animal model as it is economical with high reproducibility (Steer and Saluja, 1993) [22]. Cerulein being a cholecystokinin (CCK) analogue aids in gastric, biliary and pancreatic secretions and acts as a diagnostic tool in pancreatic malfunction and its actions are mediated by acting on the CCK1 receptor (Martin *et al*., 2005). CCK1 receptor mediates pancreatic digestive enzyme secretion when activated by cerulein in the experimental models, hyperstimulates the pancreas resulting in upregulation of inflammation mechanism *i.e.* activation of ROS and NFκB. A series of events result in the elevation of serum amylase levels, water content with cytoplasmic vacuolization at mild pace initially and shoots up with doses (Ganellin *et al*., 2005) [5]. This resembles the pathogenesis of pancreatitis with the ultimate activation of NFκB, pro-inflammatory cytokines along with histological alterations used for the induction of pancreatitis in many experimental models. Cerulein-induced acute pancreatitis histopathological findings, closely resemble those of acute pancreatitis in humans, hence this model is widely used to study the pathogenesis of acute pancreatitis in terms of intracellular enzymatic activation and mechanisms of inflammatory cell infiltration. The most widely used experimental animal model for acute pancreatitis is the cerulein-induced pancreatitis. This model utilizes rats or mice which is economical with highly reproducible results. The model is being extensively used in research findings and the mechanism of pathogenesis is well understood (Hyun and Lee, 2014) [11].

Cerulein effect on Oxidative Stress in AP
Uncontrolled stress is the important factor for pathogenesis of many diseases. Initially, the immune system tries to combat the developing stress by invading immune cells. However, the protective immune cells will be suppressed when the immune system fails with the subsequent enhancement of other pro-inflammatory cytokines like TNF-α, interleukins, etc. Enhanced progression of inflammatory cytokines leads to the organ dysfunction (Horwitz *et al.*, 2001) [9]. In mild AP caused by overstimulation with cerulein, free radical generation are mainly associated with infiltration of activated neutrophils where oxidative stress was found to be the root factor for all the ailments and disturbances observed within the body. However, disease progression and severity vary from disease to disease.

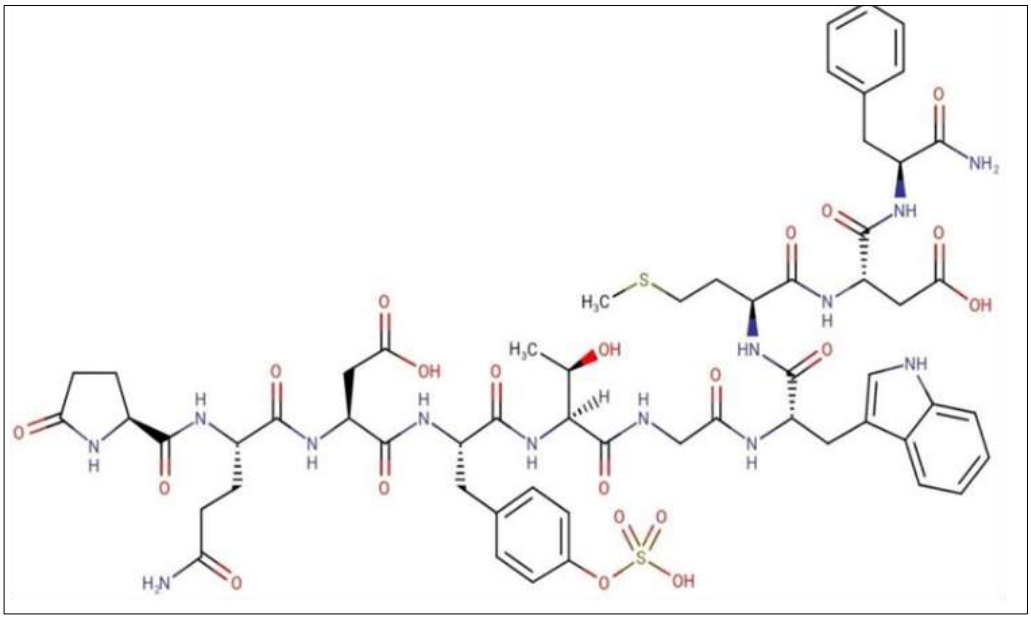
In AP, oxidative stress in pancreas damages acinar cells (Kaneto *et al.,* 1995) [12]. Oxidative stress is presently considered as a key mediator not only for the early local events associated with AP, but also of the associated SIRS (Que *et al.,* 2010) [20]. Marked depletion of reduced glutathione (GSH) in pancreas and increased lipid peroxidation in the tissue and in plasma generally reported in AP (Rau *et al.,* 2000) [21]. Increased levels of malondialdehyde (MDA) results in tissue injury. Lipid peroxidation, myeloperoxidase activity and protein carbonyls increase in plasma during AP (Hernández *et al.,* 2011) [8]. Disease severity correlates with increased superoxide radicals and lipid peroxide levels in the blood of animals with AP (Abu-Zidan *et al.,* 2000) [1]. Increased levels of MDA have also been associated with pancreatitis-associated multiple organ dysfunction syndrome (MODS). In addition, Reactive oxygen species (ROS), mainly hydroxyl radicals produce deleterious effects on mitochondrial function and DNA synthesis. Ma *et al.* (2018) found that intraperitoneal administration of cerulein (50 µg/kg b.wt) every hourly interval for eight consecutive hours in male Balb/C mice of 8-10 weeks age enhanced the Myeloperoxidase (MPO) activity with downregulation of (Superoxide dismutase) SOD activity in pancreatic tissue when compared to the normal control group. Oxidative stress and nitrosative stress play a crucial role in AP pathogenesis with altered biomarkers of antioxidant defence, nitrosative stress and lipid peroxidation.

Cerulein effect on inflammatory markers

Neoptolemos *et al.* (1998) [19] demonstrated that the activated macrophages release pro inflammatory cytokines such as IL-1β, IL-6 and TNF-α in response to the local damage to the pancreas. They also revealed that TNF-α and IL-1β are the primary cytokines initiating and propagating most consequences of SIRS in AP. In addition, they amplify the inflammatory cascade by activating mitogen -activated protein kinases (MAPK) and NFκB. NFκB activation with simultaneous activation of intracellular trypsinogen occurs early in AP (Gaiser *et al.,* 2011) [4]. NFκB is a transcription factor that plays a pivotal role in regulating the inflammatory response in mammals (Ghosh *et al.,* 1998) [6]. NFκB plays a crucial role in the pathogenesis (Baumann *et al.,* 2007) [2] which is activated both in leukocytes and within pancreatic acinar cells in AP condition (Vaquero *et al.,* 2001) [23].

Role of inflammation and Oxidative stress in the induction of Acute Pancreatitis

The key pathological events in AP remain to be the intra-pancreatic zymogen activation where the inactive trypsinogen is converted into active trypsin, dysregulated digestive enzyme secretion, vacuole accumulation, activation of inflammatory pathways leading to apoptotic and necrotic acinar cell death. The series of events in AP occur as a multistep process, initially being manifested as local limited inflammation and is amplified due to the activation of diverse inflammatory mediators such as cytokines, reactive oxygen species (ROS), chemokines, leukocyte adhesion molecules, lipids and gaseous mediators (Granger and Remick, 2005) [7]. The cellular mechanism orchestrating these mediators in the initiation of AP involves the role of key transcription factor nuclear factor kappa-B (NFκB) which regulates cytokines and adhesion molecules (Huang *et al*., 2013) [10] in addition to mitogen-activated protein kinases (MAPKs) such as p38, c-Jun N-terminal kinase (JNK), and extracellular regulated protein kinases1/2 (ERK1/2) (Murr *et al.,* 2003) [18]. In addition, during the early phase of events, abnormal cytosolic Ca^{2+} signalling also plays an important role in triggering the inflammatory pathways in the acinar cells. The injured pancreatic acinar cells and the activated immune cells in the pancreatic tissue release ROS, pro-inflammatory cytokines like TNF-α, IL-6 & IL-1β leading to oxidative stress in the pancreas which is exhibited by raise in the levels of MDA, and a decrease in the levels of SOD and GSH (Liu *et al*., 2018) [14]. Further, the released cytokines gain entry into systemic circulation leading to systemic inflammatory response syndrome (SIRS). Oxidative stress and inflammation go hand in hand in causing the severe complications of AP like SIRS which lead to distant vital organ damage of lungs, liver, and intestines and cause multiple organ dysfunction syndrome (MODS). In severe acute pancreatitis (SAP) the cascade of events includes trypsinogen activation, acinar cell death, systemic inflammatory responses, and multi-organ dysfunction (Bhatia *et al*., 2002) [3] and will ultimately lead to death.



(Source: https://go.drugbank.com/drugs/DB00403)

Fig 1: Chemical Structure of Cerulein

Conclusion

Oxidative stress and inflammation go hand in hand in causing the sequential events in Acute pancreatitis. Throughout the entire pathophysiological process, oxidative stress is well established, furthermore, the production of ROS would in turn activate the transcription factor nuclear factor kappa-B (NFκB), Activator Protein -1, STAT3, and MAPKs in the acinar cells of pancreas stimulated with cerulein. So, the entire signaling events occur between the free radical oxygen species and pro-inflammatory cytokines, which are mediated by Nuclear Factor-κB, STAT3, and MAPKs, and contribute to the inflammatory process in the pancreas.

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