Pancreatology 15 (2015) S18–S22

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Review article

Breakdown of bioenergetics evoked by mitochondrial damage in acute pancreatitis: Mechanisms and consequences

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ARTICLE INFO

Article history:
Available online 30 June 2015

Keywords:
Pancreatitis
Mitochondria
Bile acids
Ethanol
ATP
Bioenergetics

ABSTRACT

Acute pancreatitis is a severe inflammatory disease with unacceptably high mortality and without specific therapy. Clinical studies revealed that energy supplementation of patients via enteral feeding decreases systemic infections, multi-organ failure and mortality. These clinical observations have been supported by *in vitro* and *in vivo* experimental studies which showed that the most common pancreatitis inducing factors, such as bile acids, ethanol and non-oxidative ethanol metabolites induce intracellular ATP depletion and mitochondrial damage both in pancreatic acinar and ductal cells. Notably, the *in vitro* supplementation of ATP prevented the cellular damage and restored cell functions in both cell types. These observations suggest that either prevention of mitochondrial damage or restoration of intracellular ATP level might provide therapeutical benefits.

Introduction

Acute pancreatitis (AP) was the most common cause of hospitalization for non-malignant gastrointestinal diseases in the USA in 2012 leading to ~270,000 hospital admission/year with an estimated annual cost of ~2.5 billion dollars [1,2]. The majority of the cases are mild (~80%), however in the severe form (when multi-organ failure is persistent > 48 h), the mortality rate can reach as much as 40% [3]. Although AP is a severe problem, no specific pharmacological therapy is currently available. Therefore, there is a pressing economic and clinical need for developing new therapies for the treatment of AP.

During the pathogenesis of AP zymogen granules fuse with intracellular lysosomes and form autophagic vacuoles in the pancreatic acinar cells in response to direct cellular stress caused by different toxic agents (such as bile acids, ethanol and its metabolites). In the fused vacuoles cathepsin B (a lysosomal enzyme) converts trypsinogen to trypsin leading to cellular autodigestion [4]. Gaiser et al. in an elegant study used genetically engineered mice that conditionally express an endogenously activated trypsinogen within pancreatic acinar cells [5]. With this approach they provided direct evidence that intra-acinar activation of trypsinogen is sufficient to initiate AP without the activation of the immune system. They also showed that the dominant form of cell death in this model was apoptosis in the early phase of acute pancreatitis. However, necrosis, another form of cell death, is present in AP as well [6], which have been shown to correlate directly with the severity of experimental AP [7]. Notably, apoptosis is in inverse correlation with the severity, without the activation of the immune system limiting the pancreatic damage [5]. It is well documented that mitochondria play a central role in the differentiation between apoptosis and necrosis [6], since the loss of mitochondrial membrane potential ($(\Delta\Psi)_m$) and the consequent drop in the cellular ATP level promotes necrosis, whereas the release of cytochrome c from the intermembrane space promotes apoptosis. In this review we will focus on the mechanism and consequences of mitochondrial damage and breakdown of cellular bioenergetics in AP.

From the bed: clinical aspects of energy demand in acute pancreatitis

The current IAP/APA guideline for the management of AP involves fluid resuscitation, intensive care management and

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http://dx.doi.org/10.1016/j.pan.2015.06.002

highlights the importance of nutritional support in predicted severe AP [3]. According to the guideline enteral tube feeding should be the primary therapy in patients with predicted severe AP who require nutritional support. In recent years, several meta-analyses and clinical trials confirmed that enteral nutrition via nasojejunal tube feeding decreases systemic infections, multi-organ failure, need for surgical intervention, and mortality, as compared with total parenteral nutrition in patients with predicted severe AP [8,9]. The explanation for these findings embraces the facts that prolonged parenteral feeding induces atrophy and increased permeability of the gut mucosa, hypomotility of the gut due to the lack of stimulation and overgrowth of abnormal intestinal flora [10]. These pathophysiological mechanisms can lead to bacterial translocation and superinfection of the inflamed pancreatic tissue. However, a recent randomized multicentric clinical study challenged these arguments. Bakker et al. compared the early (within 24 h) nasoenteric tube feeding with an oral diet at 72 h after presentation to the emergency department in patients with AP [11]. Their primary end points were major infection (infected pancreatic necrosis, bacteremia, or pneumonia) or death during 6 months of follow-up. This study found no significant difference neither in the rate of infection, nor in the rate of death, questioning the importance of the above described beneficial effects of enteral feeding. One possible explanation for the negative outcome might be that although enteral feeding was started within 24 h, the calorie intake reached the optimal 25 kcal/kg/day only on the third day after admission in accordance with the ESPEN guidelines on parenteral nutrition [12]. However, the pathophysiological changes involving mitochondrial damage and ATP depletion are crucial early steps of the pancreatic injury during the pathogenesis of AP [13]. These facts suggest that the calorie intake in these patients should be increased sooner to compensate for the increased energy demand of AP patients.

To the bench: mitochondrial injury and intracellular ATP depletion in acute pancreatitis

Mitochondrial damage and ATP depletion have been highlighted as one of the crucial events in the development of AP [6,14,15] (Fig. 1). In an early study Nordback et al. demonstrated that the intracellular ATP levels decrease during the early phase of different experimental AP models Changes in high-energy phosphate metabolism and cell morphology in four models of acute experimental pancreatitis [16]. The most common pancreatitis inducing factors, such as bile acids, ethanol and non-oxidative ethanol metabolites cause mitochondrial damage via a complex mechanism. These agents have been shown to release Ca^{2+} from the endoplasmic reticulum (ER) and induce extracellular Ca^{2+} influx. Since mitochondria act as cellular Ca^{2+} buffers, the sustained increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), leads to mitochondrial Ca^{2+} overload and to decreased intracellular ATP ($(ATP)_i$) production. ATP is necessary for the activity of the sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) and plasma membrane Ca^{2+}-ATPase (PMCA) that remove Ca^{2+} from the cytosol. Decrease of $(ATP)_i$ impairs the cellular Ca^{2+} clearance and therefore contribute to the maintenance of sustained Ca^{2+} elevation. Prolonged mitochondrial Ca^{2+} overload can lead to the opening of the mitochondrial membrane permeability transition pore (MPTP) across the inner and outer membranes of mitochondria, resulting in an increased permeability of the mitochondrial membranes to molecules and ions with molecular mass less than 1.5 kDa, including protons and water [17]. Another possible way of mitochondrial membrane permeabilization is the mitochondrial outer membrane permeabilization (MOMP), which is supposed to be a crucial event during apoptosis and causing the release of proapoptotic factors

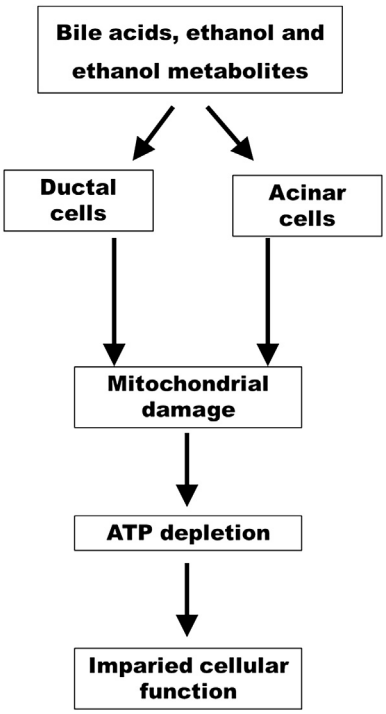

Fig. 1. Central role of mitochondrial damage in acute pancreatitis. Bile acids, ethanol and its metabolites induce mitochondrial damage both in pancreatic acinar and ductal cells. The cellular ATP level consequently decreases, which impairs a plethora of cellular functions, including cellular Ca^{2+} signaling and bicarbonate secretion in pancreatic ductal cells. The impaired cell function will lead to the development of acute pancreatitis.

from the mitochondrial intermembrane space to the cytosol [18]. The increased membrane permeability results in mitochondrial swelling and dissipation of $(\Delta\Psi)_m$, with a consequent drop in ATP production [17,19,20]. Sustained elevations of $[Ca^{2+}]_i$ and the resulting mitochondrial damage lead to a vicious cycle, which in turn triggers cell necrosis [21,22].

The role of mitochondrial injury and ATP depletion in bile acid-induced pancreatic damage

Bile acids were shown to induce Ca^{2+} release from the ER and acidic Ca^{2+} stores via inositol trisphosphate receptors (IP_3R) and ryanodine receptors (RyR) activation [23], inhibit SERCA pump activity and decrease the level of $(ATP)_i$ in pancreatic acinar cells [24,25]. On the other hand Booth et al. demonstrated that bile acids induce an increase in the intracellular and mitochondrial reactive oxygen species (ROS) production [26]. The increased ROS production promoted apoptosis and decreased necrosis. In isolated guinea pig pancreatic ductal epithelial cells (PDEC) the non-conjugated bile acid, chenodeoxycholate (CDC) induced toxic sustained Ca^{2+} increase and inhibited the activity of basolateral Na^+/H^+ exchanger, Na^+/HCO_3^- cotransporter and luminal Cl^-/HCO_3^- exchanger [27]. In these series of experiments, loading with BAPTA did not prevent the inhibitory effect of CDC on HCO_3^- secretion [28]. We also showed that CDC treatment induces morphological damage of the mitochondria and consequent $(ATP)_i$ depletion in the ductal cells [25]. Accordingly, loading pancreatic ducts with BAPTA failed to prevent the CDC-induced mitochondrial damage suggesting a Ca^{2+}-independent mechanism underlying the observed mitochondrial damage in response to CDC. In addition, ATP depletion was shown to directly inhibit pancreatic ductal HCO_3^- secretion [28].