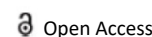




SHORT COMMUNICATION



Alteration of Bioenergetics in Pancreatic Pathophysiology

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Description

Fundamental aspect of acute pancreatitis is mitochondrial dysfunction that is Ca^{2+} -dependent. Supramaximal stimulation causes damaging global, sustained calcium elevations, in contrast to the spatially restricted, oscillatory Ca^{2+} signalling events that occur in response to physiological levels of secretagogues in isolated pancreatic acinar cells [1-3].

A primary pathological feature that is shared by known acute pancreatitis precipitants, such as bile acids, non-oxidative ethanol metabolites, and fatty acids, is the capacity to overload cytosolic Ca^{2+} and, as a result, disrupt Ca^{2+} homeostasis in acinar cells. It is also an important trigger for mitochondrial damage that compromises cellular ATP production [4,5]. Although *in vivo* studies have yielded somewhat varying results, it has long been recognized that the pancreas' altered energy levels are relevant to its pathology. Using non-invasive ^{31}P NMR spectrometry, it was discovered in early 1990 that experimental AP models had significant decreases in cellular ATP in the pancreas. It's interesting to note that responses varied depending on the model used. Consequently, levels of ATP remained constant in caerulein hyper stimulation and partial ductal obstruction models, whereas significant falls were observed in AP induced by fatty acid (oleic acid) infusion or regional ischemia. Conducted a subsequent investigation using a Clark-type electrode, Halangk and colleagues demonstrated a decrease in phosphorylating respiration in acinar cells and a decrease in ATP to 57% in caerulein AP after 24 hours, supporting these findings. It is important to note that this phenomenon developed relatively slowly. For example, the cellular ATP content reported at early

time points (up to 5 hours) was not significantly lower than that of controls, making it develop slower than other symptoms of experimental acute pancreatitis like vacuolization and intracellular trypsinogen activation [6-9].

In contrast, a recent study found that mitochondria were damaged before trypsinogen and NF κ B were activated by high levels of L-lysine. This damage could have been caused by an imbalance between hydrolysis and ATP synthesis or an impairment in electron transport chain coupling. The majority of *in vivo* models have shown that acute pancreatitis is accompanied by a loss of pancreatic ATP. This suggests that early mitochondrial damage is a significant factor in the progression of the disease [10]. Variation between studies may be due to methodological differences, the severity of the experimental model, or both. Further comparative studies are needed. As a result, the *in vivo* findings are consistent with ATP measurements made on isolated acinar cells, which showed that the concentration of ATP in cells treated with fatty acid (POA) or bile acid (TLC-S) decreased rapidly.

As a result, changes in oxygen supply and nutrient availability determined by the microcirculation will be "superimposed" on the intrinsic abilities of the exocrine cells to adjust metabolism and signalling in response to secretagogues and the inducers of acute pancreatitis discussed in the previous section. Isolated pancreatic acinar cells have been used to investigate the mechanisms underlying the ATP depletion caused by acute pancreatitis precipitants. Studies using confocal microscopy revealed that acinar cells overloaded with Ca^{2+} led to a rapid depolarization of the mitochondrial membrane potential, decreased NAD (P) H levels, increased FAD^+ levels, and necrosis. In accordance

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with stimulus-metabolism coupling (as previously mentioned), the bile acid TLCS caused predominantly oscillatory calcium rises and NADH elevations when applied at a lower concentration (200 M). However, NAD(P)H significantly decreased when sustained Ca^{2+} elevations at higher concentrations (500 M) occurred. In a similar vein, the non-oxidative ethanol metabolite Palmit-Oleic Acid Ethyl Ester (POAEE) and POA, both of which were produced by hydrolysis of the fatty acid ethyl ester, elevated cytosolic Ca^{2+} levels for an extended period of time and led to the dysfunction of mitochondria. The temporal relationship between these events was revealed by measuring cytosolic Ca^{2+} and m simultaneously; as cytosolic Ca^{2+} increased, mitochondrial depolarization and a rapid decrease in NAD(P)H were mirrored. Magnesium Green was used to measure the significant depletion of intracellular ATP that occurred as a result of mitochondrial dysfunction. The protonophore CCCP had no effect beyond its maximum. Pre-treatment with the Ca^{2+} chelator BAPTA, which prevented the loss of m while maintaining a decrease in NAD(P)H, revealed a curiously Ca^{2+} -independent action of POA. In contrast to excitable cells like cardiomyocytes, the contribution of the Na^+ /ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - exchanger to ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - homeostasis in the pancreatic acinar cell appears weak or absent. The rundown of mitochondrial ATP production has significant effects on ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - homeostasis in the pancreatic acinar cell, which appears particularly vulnerable to sustained cytosolic ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - increases. During the course of the development of acute pancreatitis, the major pathways for ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - clearance, the SERCA and PMCA pumps, which are powered by cellular ATP, would experience progressive impairment as energy levels decreased. ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - dependent mitochondrial dysfunction likely perpetuates sustained cytosolic ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - elevation, leading to increased necrotic cell death in a vicious cycle. The provision of intracellular ATP through a patch pipette demonstrated the significance of maintaining ATP levels for acinar cell function. This prevented the harmful ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - elevations induced by POA, confirming the significance of

the SERCA/PMCA for ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - clearance in pancreatic acinar cells. As a result, bile acid-induced sustained ing a decrease in NAD(P)H, revealed a curiously Ca^{2+} - rises and acinar cell necrosis were prevented by ATP, and the adverse effects of ethanol and its non-oxidative metabolites on CFTR in ductal cells that contribute to acute pancreatitis were mitigated by ATP supplementation.

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