Translational Research for Acute Pancreatitis – Which Results Have Really Influenced Our Therapy?

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Keywords

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Summary

Acute pancreatitis is a common disease characterized by acinar cell destruction and acute inflammatory changes of the pancreas that lead to a systemic inflammatory response. A major research effort has been undertaken to unravel the underlying pathophysiology and to identify possible therapeutic targets. Still, only very few findings have influenced our clinical practice in the treatment of acute pancreatitis. Pancreatic microcirculation and capillary blood flow have long been suspected to play a major role in the course of the disease. It therefore seemed tempting to speculate that manipulation of the vasoconstrictor endothelin or its antagonist nitrogen monoxide could positively influence the outcome. We had to acknowledge, however, that these mechanisms take place very early in the disease course and that only prophylactic applications show an effect; this is useful in the setting of pancreas transplantation and endoscopic retrograde cholangiopancreatography but not applicable for clinical use in the therapy of acute pancreatitis. Research then focused on later pathophysiological stages of the disease, mainly on the process of adhesion and extravasation of leukocytes into the pancreatic tissue. Here, integrins and adhesion molecules like the intercellular adhesion molecule-1 (ICAM-1) were investigated in detail. A monoclonal antibody to ICAM-1 showed promising results in experimental models but was never further evaluated in the clinical setting. Hemodilution and fluid resuscitation was

recognized to be an important therapeutic tool in acute pancreatitis. Here, initial experimental studies favored colloid solutions, and especially dextrans for isovolemic fluid resuscitation. It was recognized only later that colloid solutions are not effective and may even increase mortality in critically ill patients. Therefore, goal-directed infusion of Ringer’s lactate solution at a moderate infusion rate to optimize volume status and hemoconcentration in acute pancreatitis is now advocated. In summary, out of the numerous experimental and translational studies, only very few have really influenced our daily clinical practice. Further research is therefore needed to find more specific and effective therapeutic agents for the treatment of acute pancreatitis.

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Introduction

Acute pancreatitis is an inflammatory condition of the pancreas which causes a local and systemic inflammatory response. While most patients develop mild disease, up to 20% develop moderate to severe pancreatitis with pancreatic necrosis and/or multi-organ failure [1, 2]. The incidence has been rising in recent years, and especially the severe forms are a major clinical and financial health care burden [3]. The most common etiologic factors are gallstones and alcohol, followed by ischemia, hyperlipidemia, hypercalcemia, and hereditary factors. On a pathophysiological level, all these factors seem to primarily affect the acinar cell, resulting in the premature activation of trypsinogen and other digestive enzymes which consequently trigger the onset of the disease. A major research effort has been undertaken to unravel the precise mechanisms and to identify potential therapeutic targets in acute pancreatitis. Nevertheless, until today, only very few findings have made their way from bench to bedside and into routine clinical practice. This review focusses on these findings from translational research which have influenced our therapy of acute pancreatitis.

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Pancreatic Microcirculation – Capillary Blood Flow

Development of pancreatic edema is the first step in the pathogenesis of acute pancreatitis. In cases of mild pancreatitis, this will fully resolve over time. However, in cases of severe pancreatitis, edema will progress to peripancreatic fluid collections and pancreatic necrosis. Pancreatic microcirculation is thought to be one of the key factors that determines the course and the severity of the disease [4, 5]. This hypothesis is based on the findings of intravital microscopy in rabbits and rats which, on the one hand, showed a homogeneously increased capillary blood flow in mild pancreatitis and, on the other hand, a persistently decreased capillary perfusion in experimental necrotizing pancreatitis [6, 7]. Reduced pancreatic microcirculation in severe pancreatitis induces hypoxia of the pancreatic tissue and consequently the inflammatory cascade and tissue necrosis. Pancreatic tissue necrosis is not homogeneous, and toxic mediators that further compromise pancreatic microcirculation are released [3, 6, 8]. Interestingly, both alcohol and cigarette smoke seem to selectively impair hemoglobin oxygen saturation in the pancreas and may thereby additionally provoke pancreatic hypoxia [9, 10]. Furthermore, cigarette smoke potentiates the amount of pancreatic injury generated by ethanol alone and thus seems to be a relevant contributing factor to alcohol-induced acute pancreatitis [10].

Independent of etiology, reduced pancreatic microcirculation is based on vasoconstriction of the arterioles [6], higher flow resistance in postcapillary venules due to increased leukocyte-endothelium interactions [5, 11], arteriovenous shunts [12], and local activation of intravascular coagulation [6]. One important mechanism in the initial state of impaired microcirculation is the imbalance of endothelin and nitrogen monoxide (NO) [13]. Endothelin leads to vasoconstriction and an increased vascular permeability. Protective effects have been observed when endothelin was antagonized or NO was administered in experimental models [13]. However, these effects were only observed when treatment was given prophylactically, and no effect was observed when treatment was applied in a therapeutic approach. This finding is most likely explained by the fact that the underlying mechanisms take place in the very early phase of the disease. Therefore, inhibition of these initial processes comes too late once disease progression has started. In order to find targetable mechanisms that may allow a therapeutic intervention and therefore a possible future clinical application, leukocyte-endothelium interactions seemed to be much more promising since they occur later in the course of the disease.

Leukocyte-Endothelium Interactions

After the initial impairment of capillary blood flow through vasoactive substances like endothelin and NO, the endothelium starts to increasingly express adhesion molecules which aggravate leukocyte adhesion and extravasation [5]. Selectins account for the ‘rolling’, the first step in leukocyte adhesion, while integrins and the intercellular adhesion molecule-1 (ICAM-1) lead to the ‘stick-

ing’ and extravasation of leukocytes. This overexpression of ICAM-1 is observed much later than the initial findings of acute pancreatitis such as the activation of trypsinogen and cytokines [5, 14]. Therefore, ICAM-1 seemed to be an interesting target in acute pancreatitis, and preliminary results were promising [15]. Nevertheless, further and especially clinical studies on this target are missing, and targeting of ICAM-1 has never come to a clinical application in acute pancreatitis. Up to date, numerous studies have been undertaken to influence pancreatic capillary blood flow through various targets in pancreatitis, and some have shown promising results in experimental models in rats or mice. However, none of these specific agents have ever been shown to be effective in human acute pancreatitis. Nevertheless, one important aspect that majorly influences microcirculation and which has found its way into current clinical guidelines is early goal-directed fluid resuscitation [2, 16].

Fluid Resuscitation – Hemodilution

It is long known that fluid resuscitation is a major clinical challenge in critically ill patients. This seems to be especially the case in acute pancreatitis patients. Inflammation of the pancreas and the corresponding systemic inflammatory response leads to the extravasation of fluid to the third space with consequent hypovolemia, hypoperfusion, and organ failure. In fact, fluid resuscitation is probably the intervention that is most likely to improve clinical outcomes [17–19]. Early experimental studies have suggested that resuscitation with colloid solutions, leading to an iso-volemic hemodilution, are beneficial for pancreatic microperfusion in the setting of acute experimental pancreatitis. Various dextrans seemed to be superior to other colloid solutions [20–22], and first reports of the clinical use of dextran in severe pancreatitis were promising [23]. Only later it became clear that in critically ill patients in general, colloids should be discouraged since the evidence for their effectiveness is missing and hydroxyethyl starch may even increase mortality [24, 25]. Therefore, the current IAP/APA guideline suggests goal-directed infusion of Ringer’s lactate solution at a moderate infusion rate of 5–10 ml/kg/h since higher infusion rates and rapid hemodilution to a hematocrit of <35% in 48 h is associated with worse outcome [16]. Non-invasive clinical targets to measure fluid resuscitation are suggested as: i) heart rate < 120/min, ii) mean arterial pressure between 65 and 85 mm Hg, and iii) urinary output 0.5 ml/kg/h [16]. In this sense, evidence-based fluid resuscitation has become a lot more sophisticated in the last decades.

Conclusion

Numerous studies have investigated and largely unraveled the pathophysiology of acute pancreatitis. Despite the growing understanding of the underlying mechanisms and the evaluation of multiple potential therapeutic targets, it is still sobering to recognize

that after decades of experimental and translational studies only very few results have influenced our clinical management of acute pancreatitis. Future studies should aim to identify specific therapeutic targets in acute pancreatitis, and more effort should be made to bring these promising targets into clinical evaluation.

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