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Local Renin-Angiotensin System in the Pancreas: The Significance in Acute Pancreatitis

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Summary

Acute pancreatitis is a complex disease entity of which the pathogenesis is still not completely known. Research into the initiation and propagation of the diseases would hopefully help to design new treatment strategies for patients, especially those with severe acute pancreatitis. The novel observation of the activation of the local pancreatic renin-angiotensin system in experimental pancreatitis opens up new horizons for research regarding the pathogenesis of acute pancreatitis.

Introduction

Acute pancreatitis is a commonly encountered clinical condition although its aetiology and pathogenesis are not completely clear. Differences in the triggering mechanisms result in the same common pathway, namely, the autodigestion of pancreatic tissue by the activation of proenzymes prior to their reaching the intestinal lumen [1]. In any case, activation of the proenzymes and the subsequent release of inflammatory mediators into the interstitium, retroperitoneum and peritoneal cavity then take place.

The Clinical Problems that We Are Facing

In the clinical setting, the severity of an attack of acute pancreatitis can be mild or severe. A mild attack is usually self-limiting and the patient recovers with the resolution of the pancreatic inflammation while a severe attack is accompanied by systemic complications and multi-organ failure, which can be fatal. Although clinical, physiological and biochemical parameters exist enabling clinicians to predict the severity of an attack [2, 3], the exact pathophysiological alternations that contribute to a severe attack are largely unknown. Therefore, it is not surprising that no actual intervention is available except for supportive and intensive care therapies for those patients who have severe pancreatitis with systemic complications.

Role of Local Renin-Angiotensin System (RAS) in Acute Pancreatitis

The production and release of a variety of inflammatory mediators into the circulation have been one of the characteristic features of the systemic involvement in acute pancreatitis. Acute pancreatitis is associated with a rapid release of interleukin-1, interleukin-6 and tumor necrosis factor-alpha [4, 5]. Others mediators such as platelet activating factor, interleukin-8 and activated compliment have also been shown to be involved, however, in a rather complicated manner. Recently, the characterization of the RAS in the pancreas has been reported in laboratory animals as well as in human [6, 7, 8, 9]. The demonstration of the angiotensin II receptors and expression of key RAS component genes have consolidated the presence of such a system in the pancreas [10, 11, 12]. Furthermore, it has been shown that locally formed angiotensinogen and

angiotensin receptor subtype-specific expression increased in an animal model of acute pancreatitis [13]. As angiotensinogen and angiotensin receptors can possibly play an important role in the induction of inflammation and microcirculatory regulation in the pancreas, this may in turn contribute to pancreatic tissue injury in acute pancreatitis. Indeed, pancreatic microcirculatory changes such as vasoconstriction, capillary stasis, decreased oxygen tension, and progressive ischaemia have been shown to occur early in the course of acute pancreatitis [14]. (A more detailed description on the local RAS in pancreas could be addressed by other contributors to this Round Table).

Based on the available information, it would be logical to ask if local RAS could control or determine the extension of inflammatory activation in the pancreas, such as in the regulation of vascular injuries [15]. If this is the case, the local RAS can potentially become the target for therapy in acute pancreatitis.

Discussion

Recent findings in the field of the local RAS in the pancreas have opened up new horizons for research regarding the pathophysiology of acute pancreatitis. However, there are a few important questions to be answered before we can put this information to use. Firstly, what is the downstream pathway after the activation of the local RAS in acute pancreatitis? Out of the many known and unknown mediators of the inflammatory process, it does not seem to be an easy task to determine the downstream mediator(s) which are regulated by the local RAS. Furthermore, data on the effects of blocking local RAS activation in models of acute pancreatitis is lacking. Molecules in the families of reactive oxygen metabolites and reactive nitrogen species have been shown to be mediated by RAS in the circulatory system [16, 17]. Nitric oxide is known to increase pancreatic secretion as well as improve pancreatic perfusion [18] while reactive oxygen metabolites are important mediators in ischaemic-reperfusion injury [19]. Obviously their roles in acute pancreatitis in relation to the local RAS remain to be investigated. Secondly, what is the relationship between the activation of local RAS in the pancreas and the circulating RAS? Activation of the plasma RAS as shown by an elevation of plasma renin has been demonstrated in patients with acute pancreatitis [20]. Although the circulatory hypovolaemia was thought to be the main cause for the activation of plasma RAS, it is tempting to hypothesize with the knowledge of the existence of the local RAS that activation of local RAS may be related to the plasma RAS, either directly or through other inflammatory mediators. Further animal and human studies would hopefully clarify the relationship between the local and plasma RAS in acute pancreatitis.

Conclusion

The pathophysiology of acute pancreatitis is a complex subject. However, it is vitally important to determine the relevant pathophysiological pathways before an effective treatment of the condition can be designed. The recent notion of a local RAS or possibly a circulating RAS in acute pancreatitis has opened up a new and exciting horizon for future research in the field of pancreatitis.

Key words Angiotensinogen; Angiotensins; Receptors, Angiotensin

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