JOP. J Pancreas (Online) 2003; 4(2):89-91.

Pancreatic Renin-Angiotensin System: A Novel Target for the Potential Treatment of Pancreatic Diseases?

Po Sing Leung

Department of Physiology, Faculty of Medicine, The Chinese University of Hong Kong. Shatin, Hong Kong

The hormonal renin-angiotensin system (RAS) has important physiological functions, which are related directly and indirectly to the regulation of blood pressure, fluid and electrolyte balance [1]. The potent vasoconstrictor action of angiotensin II (Ang II) originates from hepatic precursor angiotensinogen, where it is cleaved by the renal enzyme renin in the circulating blood. The product, Ang I, is subsequently hydrolyzed to Ang II by the pulmonary angiotensin converting-enzyme (ACE). However, alternate enzymes to renin and ACE can generate different RAS products called angiotensins in addition to Ang II including Ang III, Ang IV and Ang (1-7). The resultant angiotensins exert their physiological actions via their specific receptors, namely AT_1, AT_2, AT_4, and AT_7 respectively. In this regard, a homologue of ACE, termed ACE2, has recently been identified and shown to be an essential regulator of heart function [2]. Unlike ACE, ACE2 acts as a carboxypeptidase on Ang II yielding Ang (1-7). Ang II can be also converted into Ang III and Ang IV by aminopeptidases. Ang IV binds at the AT_4 receptor which affects learning and memory and cognitive functions [3].

Recently, it has been demonstrated that many tissues/organs exhibit their own RAS products and activities. Such an intrinsic RAS can cater to specific local functions of their respective tissues/organs which are different from, complimentary or counteracting to the hormonal RAS, frequently in a paracrine and/or autocrine action [4]. They include cell proliferation, anti-proliferation, apoptosis, superoxide generation, and vasoconstriction as well as vasodilatation.

These actions, as it has recently been found in the literature, extend beyond the nervous and cardiovascular systems and include such diverse targets as the pancreas [5].

In the pancreas, previous studies have made an incremental but significant advance in the knowledge of the expression, localization, regulation and potential function of a pancreatic RAS. It has been demonstrated that major components of such a local pancreatic RAS are responsive to a number of physiological stimuli and clinical conditions [6]. The available data indicate that a pancreatic RAS would be important for regulating the exocrine and endocrine functions such as acinar digestive enzyme secretion, islet hormonal secretion and ductal anion secretion. Aberrations from a normal regulation of a pancreatic RAS may be of clinical relevance in some pancreatic diseases. In this regard, a collection of up-to-date publications which specifically address the potential role of the pancreatic RAS and its clinical implications was available in a round-table discussion published in JOP. J Pancreas [7].

In terms of an exocrine pancreas, it has previously been shown that acute pancreatitis could markedly upregulate the expression of RAS components thus implicating its clinical relevance to pancreatitis [8]. In this respect, recent findings have further demonstrated that

the administration of RAS inhibitors, such as antagonist for Ang II receptors in cerulein-induced pancreatitis, could be protective against the severity of pancreatic injury. This implies that activation of a pancreatic RAS in acute pancreatitis plays a role in pancreatic tissue injury [9]. Interestingly, the administration of RAS inhibitors could ameliorate oxidative stress and tissue injury in cerulein-induced pancreatitis [10]. Such a protective effect may open up a new strategy in the treatment of pancreatitis by virtue of using Ang II receptor antagonists rather than antioxidant therapy. Interestingly, a recent study has demonstrated that Ang II can activate calcium-mediated chloride channels in both cystic fibrosis and pancreatic epithelial cells, indicating a role for pancreatic RAS in regulating pancreatic ductal secretion and its clinical relevance to cystic fibrosis [11].

The endocrine role of pancreatic RAS in the regulation of islet blood flow thus affecting insulin secretion by pancreatic islet cells has previously been reported [12]. In this respect, our preliminary data have demonstrated that major RAS components were expressed in endogenous pancreatic islet cells and the AT_1 receptor was specifically localized to insulin-secreting beta cells. In addition, AT_1 receptor was subjected to upregulation in transplanted islets, indicating the significance of islet RAS in islet hormonal secretion through graft function [13]. Interestingly, Ang II was observed to decrease, in a dose-dependent manner, the insulin release by isolated pancreatic islet cells, which was inhibitable by losartan, an AT_1 receptor antagonist (unpublished data). These data indicate that a pancreatic RAS may play a role in regulating islet hormonal secretion, which should be clinically relevant to diabetes mellitus. On the other hand, a recent study has demonstrated that a local pancreatic RAS was subjected to regulation by pancreatic endocrine tumour (PET) and the significance of the changes may have implications in patients with PET [14]. Of great interest in this context are recent findings that the AT_4 receptor is the enzyme insulin-regulated aminopeptidase, suggesting its potential role in glucose uptake [15]. Whether or not the AT_4 receptor is present in the pancreas and its potential role in diabetes mellitus need intensive investigation.

As far as the pancreas is concerned, the most significant disorders of the exocrine pancreas are acute and chronic pancreatitis, adenocarcinoma and cystic fibrosis while the main disorders of the endocrine pancreas are diabetes mellitus and islet cell tumors. The immediate question is whether a future target for a pancreatic RAS, using specific RAS blockers, could provide a novel pathway for the potential treatments of some exocrine and endocrine pancreatic diseases. Alternatively, the development of the potential use of some agents from natural sources such as herbal medicines could be promising in manipulating the pancreatic RAS. To this end, considerable bricks should be added to this fascinating building of a pancreatic RAS.

Key words Cystic Fibrosis; Diabetes Mellitus; Islets of Langerhans Transplantation; Pancreas; Pancreatitis; Renin-Angiotensin System

Abbreviations ACE: angiotensin converting-enzyme; Ang: angiotensin; AT: angiotensin receptor type; PET: pancreatic endocrine tumor; RAS: renin-angiotensin system

Acknowledgements The work in this paper was fully supported by a grant from the Research Grants Council of Hong Kong (Project no. CUHK 4075/00M & 4116/01M)

Correspondence
Po Sing Leung
Department of Physiology
Faculty of Medicine
The Chinese University of Hong Kong
Shatin, New Territories
Hong Kong
Phone: +852-2609.6978
Fax: +852-2603.5022
E-mail address: psleung@cuhk.edu.hk

References

1. Reid IA, Morris BJ, Ganong WF. The renin-angiotensin system. Ann Rev Physiol 1978; 40:377-410. [PMID 205167]

2. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002; 417:822-8. [PMID 12075344]

3. Wright JW, Harding JW. Important role for angiotensin III and IV in the brain–angiotensin system. Brain Res Brain Res Rev 1997; 25:96-124. [PMID 9370053]

4. Leung PS. Intrinsic angiotensin-generating system: its tissue specific functions and clinical implications. Panminerva Med 2002; 44:93-7. [PMID 12032426]

5. Leung PS, Chappell MC. A local pancreatic renin-angiotensin system: endocrine and exocrine roles. Int J Biochem Cell Biol 2003; 35:834-46.

6. Leung PS, Carlsson PO. Tissue renin-angiotensin system: its expression, localization, regulation and potential role in the pancreas. J Mol Endocrinol 2001; 26:155-64. [PMID 11432370]

7. Leung PS, ed. Renin-angiotensin system in the pancreas: from the basic research to the bedside. JOP. J Pancreas (Online) 2001; 2:1-57.

8. Leung PS, Chan WP, Nobiling R. Regulated expression of pancreatic renin-angiotensin system in experimental pancreatitis. Mol Cell Endocrinol 2000; 166:121-8. [PMID 10996430]

9. Tsang SW, Ip SP, Wong TP, Che CT, Leung PS. Differential effects of saralasin and ramiprilat, the inhibitors of renin-angiotensin system, on cerulein-induced acute pancreatitis. Regul Pept 2003; 111:47-53.

10. Ip SP, Tsang SW, Wong TP, Che CT, Leung PS. Saralasin, a non-specific angiotensin II receptor antagonist, attenuates oxidative stress and tissue injury in cerulein-induced acute pancreatitis. Pancreas 2003; 26 (in press).

11. Fink AS, Wang Y, Mendez T, Worrell R, Eaton D, Nguyen T, Lee SP. Angiotensin II evokes calcium-mediated signaling events in isolated dog pancreatic epithelial cells. Pancreas 2002; 25:290-5. [PMID 12370541]

12. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. Diabetologia 1998; 41:127-33. [PMID 9498644]

13. Lau T, Carlsson PO, Leung PS. Expression of islet renin-angiotensin system and its regulation in islet transplants. Taiwan-Hong Kong Annual Physiology Symposium 2002. Kaohsiung, Taiwan: 19-20 October, 2002. Kaohsiung, Taiwan: Kaohsiung Medical University, 2002.

14. Lam KY, Leung PS. Regulation and expression of a renin-angiotensin system in human pancreas and pancreatic endocrine tumours. Eur J Endocrinol 2002; 146:567-72. [PMID 11916627]

15. Albiston AL, McDowall SG, Matsacos D, Sim P, Clune E, Mustafa T, et al. Evidence that the angiotensin IV (AT4) receptor is the enzyme insulin-regulated aminopeptidase. J Biol Chem 2001; 276:48623-6. [PMID 11707427]