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Local Renin-Angiotensin System in the Pancreas: The Significance of Changes by Chronic Hypoxia and Acute Pancreatitis

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Summary

The circulating renin-angiotensin system (RAS) plays an important role in the maintenance of blood pressure and fluid homeostasis. Recently, there has been a shift of emphasis from the circulating RAS to the local RAS in the regulation of individual tissue functions via a paracrine and/or autocrine mechanism. In fact, a local RAS has been proposed to be present in an array of tissues including the brain, heart, kidney and gonads. Our previous studies have provided solid evidence that several key elements of the RAS, notably angiotensinogen and renin, are present in the rat pancreas. The data support the existence of an intrinsic RAS in the pancreas and this local RAS may be important for the exocrine/endocrine functions of the pancreas. Interestingly, such a pancreatic RAS has been demonstrated to be markedly activated by experimental rat models of chronic hypoxia and acute pancreatitis. The activation of the pancreatic RAS by chronic hypoxia and experimental pancreatitis could play a role in the physiology and pathophysiology of the pancreas. The significant changes of pancreatic RAS may have clinical relevance to acute pancreatitis and hypoxia-induced injury in the pancreas.

Introduction

The circulating renin-angiotensin system (RAS) plays a crucial endocrine role in the physiology of blood pressure and electrolyte balance [1]. Recently, there has been a shift of emphasis from an endocrine role of RAS to an autocrine/paracrine control of tissue functions which is becoming critical to the understanding of regulatory mechanisms in individual tissues. The presence of key RAS component genes particularly at the level of angiotensinogen and renin which, in turn, are indispensable for the existence of a local RAS in a variety of tissues, has been previously documented [2, 3, 4]. The existence of locally formed RAS components in multiple tissues including the brain, heart, kidney and gonads has led to the assumption that angiotensin II may act as a local hormone. It may either potentiate the systemic functions or have entirely separate activities which meet the tissue needs [5, 6]. In the reproductive tissues, a local RAS has been proposed and it may be important in the regulation of various reproductive functions [7, 8, 9]. Such a local RAS has been recently reported in the rat epididymis [10, 11] with a paracrine or autocrine control of epididymal and sperm functions [12]. Interestingly, the gene expression of the epididymal RAS was regulated developmentally [13] as well as by testicular-hormones [14].

Pancreatic RAS and its Potential Functions

In the pancreas, the notion of a local RAS and its potential role have been previously reported in the

dog [15, 16], the rat [17] and in humans [18]. The data suggested that the pancreatic RAS may play an autocrine/paracrine role in the regulation of the endocrine/exocrine functions of the pancreas. The RAS has recently been shown to regulate islet blood flow and thus the endocrine function of insulin secretion in the rat pancreas [19]. The effect of the RAS on oxygen tension and blood flow in transplanted pancreatic islets were also demonstrated [20]. In addition, the RAS was highly activated in shock states and was suggested to be involved in the pathophysiology of the markedly deteriorated splanchnic circulation including the pancreas [21].

The existence of a pancreatic RAS and its potential role in the regulation of exocrine function have been studied in our laboratory. Our previous studies showed that angiotensin II receptor subtypes, namely AT_1 and AT_2 [22] and angiotensin II [23] were predominantly localized in the epithelia and endothelia of the pancreatic ducts and blood vessels respectively of the rodent pancreas. The existence of such a pancreatic RAS has been further consolidated based on the expression and localization of key RAS component genes, which were localized coincidentally in the endothelia of the vasculature and epithelia of pancreatic ducts [24]. All these data suggest that a pancreatic RAS may play a paracrine/autocrine role in the regulation of pancreatic microcirculation and ductal anion secretion. In fact, our recent results have demonstrated that such a local RAS could mediate pancreatic blood flow (data not yet published) and ductal anion secretion [25] in the rat pancreas.

Activation of Pancreatic RAS by Chronic Hypoxia and by Acute Pancreatitis

The regulation of the major RAS component genes is controlled by an array of factors such as hormones, ions and stress [6]. One of these factors, namely hypoxic stress has been shown to result in the activation of the local RAS in tissues including the kidney [26], lung [27] and heart [28]. These data suggest that activation of the RAS by chronic hypoxia should be important for the physiological and pathophysiological changes of these tissue functions. It has been thought that prolonged hypoxia causes decreased blood flow to the tissues, which may in turn lead to tissue inflammation and injury. For example, alcohol was believed to induce hypoxia in the pancreas which could, in turn, provide a mechanism for pancreatic injury such as pancreatitis [29]. It has also been shown that angiotensin II-mediated selective pancreatic vasoconstriction results in significant pancreatic ischemia/hypoxia during exposure to stress such as cardiogenic shock [30]. In fact, chronic hypoxia has been known to cause some forms of tissue injury such as inflammatory synovitis [31]. However the influence of hypoxia on the pancreatic RAS and its pathophysiological significance are far less clear. Interestingly, our recent study demonstrated that the pancreatic RAS was subject to the activation by chronic hypoxia, notably at the levels of its locally formed angiotensinogen, AT_{1b} and AT_2 receptor subtypes [32]. Such activation of pancreatic RAS by chronic hypoxia could play a role leading to hypoxia-induced pancreatic injury such as acute pancreatitis.

Although the etiology of acute pancreatitis is believed to be multifactorial, the activation of proteolytic enzymes, lipase, kinins and other active peptides may be some of the crucial mediators responsible for alterations of RAS expression [33, 34]. In fact, previous studies have shown that the activity of the plasma RAS significantly increased in acute pancreatitis [35, 36]. In addition, the severity of acute pancreatitis is correlatively associated with the impairment of pancreatic microcirculation [37]. Nevertheless, the association between acute pancreatitis and the RAS, with particular reference to a local RAS in the pancreas, has received little attention. Interestingly, our recent study established this linkage by showing that acute pancreatitis dramatically induces the expression of the pancreatic RAS components, particularly the

angiotensinogen, and AT_{1a} and AT_2 receptor subtypes [38]. Such activation could play a role in the pathophysiology of acute pancreatitis.

The Role of RAS in the Regulation of Free Radicals and Apoptosis, and its Implications to the Pancreatic Injury

The data prompt us to speculate that the activation of the pancreatic RAS by chronic hypoxia and by acute pancreatitis could have a prominent role in the physiology and possible pathophysiology of the pancreas. Inflammation/injury of the pancreas can be initiated by several means, including excess alcohol intake, probably involving an alcohol-induced hypoxia mechanism [29], pancreatic duct obstruction resulting from a migrating gallstone, pancreatic ischemia/hypoxia [30] or by a vast array of mediators [39, 40]. One significant feature of many of these mediators, however, is that reactive oxygen species (ROS) and reactive nitrogen species (RNS) may be involved in their mechanism of action and free radicals are known to induce apoptotic cell death in various cell types such as endothelial and smooth muscle cells [41]. In the pancreas, free radicals were also previously reported to be involved in the pathophysiology of acute pancreatitis [42].

The RAS has recently been shown to play a role in mediating the ROS and RNS species in various cell types such as the vascular cells [43, 44]. Moreover, RAS, in particular with the AT_2 receptor subtype, was previously addressed in the regulation of vascular injury [45] and in the control of apoptosis [46]. Although the physiological role of AT_2 receptor subtype in many tissues, especially in the pancreas remains unsettled, the upregulation of this receptor subtype is associated with apoptotic cell death and pathogenesis in tissues including the heart [47, 48], lung [49] and ovary [50]. Interestingly, the ROS were reported to be synthesized by endothelial and vascular smooth muscle cells using NADPH oxidase and, in turn, angiotensin II could stimulate enhanced ROS production via the increased activity of NADPH oxidase [51]. The role of the RAS in the regulation of the ROS via increased activity of NADPH oxidase and the role of vascular apoptotic cell death in the pathogenesis of atherosclerosis have recently been demonstrated [52, 53]. Nevertheless, the significance of activation of the pancreatic RAS and its association with the regulation of free radicals and apoptosis in the pancreas has yet to be investigated.

Conclusion

Our recent studies, which focused on the pancreas, have provided solid evidence for the presence of a local RAS in the pancreas, which may be important for the regulation of the exocrine/endocrine functions of the pancreas. Such a pancreatic RAS was subject to activation by chronic hypoxia and acute pancreatitis. The significance of the activation of the pancreatic RAS by chronic hypoxia and acute pancreatitis, and its role in the induction of free radicals and apoptotic cell death in the pancreas may have physiological and pathophysiological relevance to the pancreas.

Key words Angiotensinogen; Anoxia; Pancreas; Pancreatitis; Renin-Angiotensin System

Abbreviations AT_1: angiotensin II receptor type 1; AT_2: angiotensin II receptor type 2; RNS: reactive nitrogen species; ROS: reactive oxygen species

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References

1. Peach MJ. Renin-angiotensin system: biochemistry and mechanisms of action. Physiol Rev 1977; 57:313-70.

2. Campbell DJ, Habener J. Angiotensinogen gene is expressed and differentially regulated in multiple tissues of the rat. J Clin Invest 1986; 78:31-9.

3. Deschepper CF, Mellon SH, Cumin F, Baxter JD, Ganong WF. Analysis by immunocytochemistry and in situ hybridization of renin and its mRNA in kidney, testis adrenal, and pituitary of the rat. Proc Natl Acad Sci USA 1986; 83:7552-6. [87016987]

4. Dzau VJ, Ellison KE, Brody T, Ingelfinger J, Pratt E. A comparative study of the distribution of renin and angiotensinogen messenger ribonucleic acids in rat and mouse tissues. Endocrinology 1987; 120:358-64.

5. Dzau VJ, Burt DW, Pratt RE. Molecular biology of the renin-angiotensin system. Am J Physiol 1988; 255:F563-73.

6. Phillips MI, Speakman EA, Kimura B. Levels of angiotensin and molecular biology of the tissue renin-angiotensin system. Regul Pept 1993;43:1-20. [93150166]

7. Ganong WF. Reproduction and the renin-angiotensin system. Neurosci Biobehav Rev 1995; 19:241-50. [95357004]

8. Vinson GP, Saridogan E, Puddefoot JR, Djahanbakhch O. Tissue renin-angiotensin systems and reproduction. Hum Reprod 1997; 12:651-62. [97302988]

9. Speth RC, Daubert DL, Grove KL. Angiotensin II: a reproductive hormone too? Regul Pept 1999; 79:25-40. [99127770]

10. Leung PS, Chan HC, Fu LXM, Leung PY, Cheng-Chew SB, Wong PYD. Angiotensin II receptors: localization of type I and type II in rat epididymides of different developmental stages. J Membr Biol 1997; 157:97-103. [97286499]

11. Leung PS, Wong TP, Sernia C. Angiotensinogen expression by rat epididymis: evidence for an intrinsic, angiotensin-generating system. Mol Cell Endocrinol 1999; 155:115-22. [20046811]

12. Leung PS, Chan HC, Fu LXM, Zhou WL, Wong PYD. Angiotensin II receptors, AT_1 and AT_2 in the rat epididymis: immunocytochemical and electrophysiological studies. Biochim Biophys Act 1997; 1357:65-72.

13. Leung PS, Yao XQ, Chan HC, Fu LXM, Wong PYD. Differential gene expression of angiotensin II receptor subtypes in the epididymides of mature and immature rats. Life Sci 1998; 62:461-8.

14. Leung PS, Wong TP, Lam SY, Chan HC, Wong PYD. Testicular hormonal regulation of the renin angiotensin system in the rat epididymis. Life Sci 2000; 66:1317-24.

15. Chappell MC, Milsted A, Diz DI, Brosnihan KB, Ferrario CM. Evidence for an intrinsic angiotensin system in the canine pancreas. J Hypertens 1991; 9:751-9. [92012988]

16. Chappell MC, Diz DI, Jacobsen DW. Pharmacological characterization of angiotensin II binding sites in the canine pancreas. Peptides 1992; 13:311-8. [93027675]

17. Ghiani BU, Masini MA. Angiotensin II binding sites in the rat pancreas and their modulation after sodium loading and depletion. Comp Biochem Physiol A Physiol 1995; 111:439-44. [95338780]

18. Tahmasebi M, Puddefoot JR, Inwang ER, Vinson GP. The tissue renin-angiotensin system in human pancreas. J Endocrinol 1999; 161:317-22. [99271012]

19. 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. [98158409]

20. Carlsson PO, Palm F, Andersson A, Liss P. Chronically decreased oxygen tension in rat pancreatic islets transplanted under the kidney capsule. Transplantation 2000; 69:761-6. [20216299]

21. Oldner A, Wanecek M, Weitzberg E, Rundgren M, Alving K, Ullman J, Rudehill A. Angiotensin II receptor antagonism increases gut oxygen delivery but fails to improve intestinal mucosal acidosis in porcine endotoxin shock. Shock 1999; 11:127-35.

22. Leung PS, Chan HC, Fu LX M, Wong PYD. Localization of angiotensin II receptor subtypes AT_1 and AT_2 in the pancreas of rodents. J Endocrinol 1997; 153:269-74. [97308925]

23. Leung PS, Chan HC, Wong PYD. Immunohistochemical localization of angiotensin II in the mouse pancreas. Histochem J 1998; 30:21-5. [98198607]

24. Leung PS, Chan WP, Wong TP, Sernia C. Expression and localization of renin-angiotensin system in the rat pancreas. J Endocrinol 1999; 160:13-9. [99077887]

25. Chan HC, Law SH, Leung PS, Fu LX, Wong PYD. Angiotensin II receptor type I-regulated anion secretion in cystic fibrosis pancreatic duct cells. J Membr Biol 1997; 156:241-50. [97252709]

26. Neylon M, Marshall J, Johns EJ. The role of the renin-angiotensin system in the renal response to moderate hypoxia in the rat. J Physiol 1996; 491:479-88.

27. Morrell NW, Atochina EN, Morris KG, Danilov SW, Stenmark KR. Angiotensin converting enzyme is increased in small pulmonary arteries of rats with hypoxia-induced pulmonary hypertension. J Clin Invest 1995; 96:1823-33.

28. Morrell NW, Danilov SW, Satyan KB, Morris KG, Stenmark KR. Right ventricular angiotensin converting enzyme activity and expression is increased during hypoxic pulmonary hypertension. Cardiovasc Res 1997; 34:393-403.

29. Foitzik T, Castillo F, Rattner DW, Klar E, Warshaw AL. Alcohol selectively impairs oxygenation of the pancreas. Arch Surg 1995; 130,357-61. [95225721]

30. Reilly PM, Toung TJ, Miyachi M, Schiller HJ, Bulkley GB. Haemodynamics of pancreatic ischemia in cardiogenic shock. Gastroenterology 1997; 113:938-45. [97434101]

31. Bodamyali T, Stevens CR, Billingham MEJ, Ohata S, Blake DR. Influence of hypoxia in inflammatory synovitis. Ann Rheum Dis 1998; 57:703-10.

32. Chan WP, Fung ML, Nobiling R, Leung PS. Activation of local renin-angiotensin system by chronic hypoxia. Mol Cell Endocrinol 2000; 160:107-14. [20181765]

33. Agarwal N, Pitchumoni CS. Acute pancreatitis: a multisystem disease. Gastroenterologist 1993; 1: 115-128. [94326122]

34. Lembeck F, Griesbacher T. Pathophysiological and possible roles of kinins in the pancreas. Immunopharmacology 1996; 33:336-8.

35. Greenstein RJ, Krakoff LR, Felton K. Activation of the renin system in acute pancreatitis. Am J Med 1987; 82:401-4. [87153404]

36. Pitchumoni CS, Agarwal N, Jain NK. Systemic complications of acute pancreatitis. Am J Gastroenterol 1988; 83:597-606.

37. Bassi D, Kollias N, Fernandez-del Castillo C, Foitzik T, Warshaw AL, Rattner DW. Impairment of pancreatic microcirculation correlates with severity of acute experimental pancreatitis. J Am Coll Surg 1994; 179:257-63.

38. Leung PS, Chan WP, Nobiling R. Regulated expression of pancreatic renin-angiotensin system in experimental pancreatitis. Mol Cell Endocrinol 2000; 166:121-8. [20453048]

39. Niederau C, Luthen R. Events inside the pancreatic acinar cell in acute pancreatitis: role of secretory blockade, calcium release and dehydration for the initiation of trypsinogen activation and autodigestion. In: Lankisch PG, DiMagno EP, Eds. Pancreatic Disease. Berlin: Springer-Verlag, 1999: 14-23.

40. Pezzilli R, Billi P, Miniero R, Barakat B. Serum interleukin-10 in human acute pancreatitis. Dig Dis Sci 1997; 42:1469-72. [97388815]

41. Jacobson MD. Reactive oxygen species and programmed cell death. Trends Biochem Sci 1996; 21:83-8. [97036932]

42. Schulz HU, Niederau C, Klonowski-Stumpe H, Halangk W, Luthen R, Lippert H. Oxidative stress in acute pancreatitis. Hepatogastroenterology 1999; 46:2736-50. [20041758]

43. Fernandez-Alfonso MS, Gonzalez C. Nitric oxide and the renin-angiotensin system: is there a physiological interplay between the system? J Hypertens 1999; 17:1355-61. [99454018]

44. Berry C, Hamilton CA, Brosnan MJ, Magill FG, Berg GA, McMurray JJV, Dominiczak AF. Investigation into the sources of superoxide in human blood vessels: angiotensin II increases superoxide production in human internal mammary arteries. Circulation 2000; 101:2206-12. [20263651]

45. Janiak P, Pillon A, Prost JF, Vilaine JP. Role of angiotensin subtype 2 receptor in neointima formation after vascular injury. Hypertension 1992; 20:737-45. [93084295]

46. Yamada T, Horiuchi M, Dzau VJ. Angiotensin II type 2 receptor mediates programmed cell death. Proc Natl Acad Sci USA 1996; 93:156-160. [96133896]

47. Leri A, Liu Y, Li BS, Fiordaliso F, Malhotra A, Latini R, et al. Upregulation of AT_1 and AT_2 receptors in postinfarcted hypertrophied myocytes and stretch-mediated apoptotic cell death. Am J Pathol 2000; 156:1663-72.

48. De Mello WC, Danser AHJ. Angiotensin II and the heart: on the intracrine renin angiotensin system. Hypertension 2000; 35:1183-8.

49. Bargout R, Jankov A, Dincer E, Wang RQ, Komodromos T, Ibarra-Sungao, et al. Amiodarone induces apoptosis of human and rat alveolar epithelial cells in vitro. Am J Physiol Lung Cell Mol Physiol 2000;

278:L1039-44. [20245907]

50. Kotani E, Sugimoto M, Kamata H, Fujii N, Saitoh M, Usuki S, et al. Biological roles of angiotensin II via its type 2 receptor during rat follicle atresia. Am J Physiol 1999; 276:E25-33. [99103897]

51. Griendling KK, Ushio-Fukai M. Reactive oxygen species as mediators of angiotensin signaling. Regul Pept 2000; 91:21-7. [20425229]

52. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth cells. Circ Res 1994: 74:1141-8.

53. Dimmeler S, Zeiher M. Reactive oxygen species and vascular cell apoptosis in response to angiotensin II and pro-atherosclerotic factors. Regul Pept 2000; 90:19-25. [20291327]