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The Renin-Angiotensin System: From the Renal Basis to an Organ-Specific Subsystem in the Pancreas

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Summary

Not only is the renin–angiotensin system or its components found morphologically in many organs, it also exerts many different regulatory functions such as contributing to systemic homeostasis as well as to organ-specific regulation.
The presence of the components of the renin–angiotensin system in the pancreas was discovered only a few years ago. Physiological and pathophysiological stimuli were able to modify, in part, the gene expression and the occurrence of some of these components. Because of the important clinical significance of pancreatic diseases such as pancreatitis, research should follow every traces of the renin–angiotensin system in the pancreas: impairment of microcirculation via hypoxia mediated up-regulation with the subsequent further deterioration of the oxygen supply seems to be the most obvious mechanism.
There are many possible approaches to a better understanding of problems that are associated with diseases such as different kinds of pancreatitis; basic studies in animal models are oriented toward microcirculation, cellular function and the time course of modified gene expression after stimuli such as hypoxia; a clinical approach must reevaluate different correlations between clinical parameters of hypertension and those of pancreatic diseases.

Introduction

The renin-angiotensin system (RAS) has long been described as an important regulatory system for blood pressure and blood volume. Renin, being the key regulatory component, is located mainly in the preglomerular arterioles of the kidney, but many organ-specific local RAS have been described and/or suspected in the last two decades. The best-studied extrarenal RAS is located in the brain and also, for example, in the placenta and heart. Its effector peptide angiotensin II regulates tissue blood flow via vasoconstriction. In addition, the release of neurotransmitters and hormones can be stimulated by angiotensin II. Consequently, there is increasing evidence that its endocrine functions are not limited only to the volume regulatory pathway via stimulation of aldosterone secretion and subsequent tubular sodium reabsorption. Hence, the RAS potentially has a role in almost all tissues. The existence of a local RAS in the pancreas was suspected a few years ago, and since then, an increasing number of observations on this specific RAS have entered the discussion. The aim of this contribution is to add evidence for the potential clinical importance of the pancreatic RAS. An initial observation on alterations of the physiological pattern of the RAS components during experimental pancreatitis underlines a more than academically interesting role of the RAS in clinical problems of the pancreas.

Current Basic Evidence for the Importance of the RAS

Many textbooks of physiology describe the RAS as one of the most important systems that combines the regulation of blood pressure with that of volume [1, 2, 3]. This view has emerged and was accepted decades ago; renin from the kidney was recognized early on as the regulating hormone [4] and it was found to be located mainly in the distal part of the afferent arteriole, close to the glomerulus [5]. Functional studies, including morphology [6, 7, 8], electrophysiology [9], microcirculation [10], and biochemistry [11] extended the knowledge regarding the cellular basis of systemic function of the renal part of the RAS. An improved understanding of the characteristics of the secretory mechanisms resulted in new concepts concerning the function of the juxtaglomerular apparatus [12].

These intensive investigations had additional consequences: besides the aspects of systemic regulation such as sympathetic tone or blood pressure [13, 14], current evidence indicates that organ-specific or even cell-specific RAS exist that exert local regulatory capabilities. An example is the observation made by Taugner *et. al.* that angiotensin II is co-localized with renin in mature secretory vesicles of the renin synthesizing cells [15, 16]. Hence, a very short negative feedback loop exists between renin secretion and angiotensin II mediated depolarization and subsequent inhibition of secretion in these cells. As a consequence, the frequency of extrusion of renin containing granules even under stimulating conditions is extremely low: the observations give a number of about less than 2-3 exocytotic events per hour and cell. Moreover, microcirculation studies have opened novel insights into blood vessel function mediated by various stimulating and inhibiting drugs that are associated with the RAS, such as sympathetic transmitters, and the respective inhibitors [17, 18].

Findings regarding the local RAS in many organs were successful particularly in brain and heart. Both organs play important roles in maintaining the circulation and regulating the blood pressure. For example, the central nervous system was subject to intensive research of RAS components, in particular of all types of angiotensin receptors [19].

Recently, evidence has been emerging that the pancreatic RAS can be influenced by pathological situations such as hypoxia [20] or pancreatitis [21]. Whereas hypoxia may represent a more physiological stimulus, pancreatitis is an extremely severe clinical complication that is lethal in up to 80% of the cases. Therefore, the interpretations of both observations must originate from different basic viewpoints.

Hypoxia could be caused by transient stays at high altitudes or by every-day breathing problems. This stimulus therefore is a result of nearly physiological situations. It may lead to an increased production of acidic metabolites and subsequent decrease of plasma pH. As a consequence, vasodilatation will occur in many vascular beds. Hence, up-regulation of components of the RAS could be interpreted as a contribution to systemic and/or local negative feedback that maintains blood supply as well as blood pressure.

This is completely different in pancreatitis as a clinical complication; it is far from a regulatory situation, an up-regulation under these circumstances would cause positive feedback which leads to severe deficiency in blood supply. Pancreatitis research requires the development of pathological animal models [22] that may be helpful in a better understanding the heterogenic clinical occurrence of pancreatitis. Up to now, we know that this disease is mostly associated with impairment of microcirculation, including all consequences of local inflammatory processes.

Future Basic Perspectives

The first evidence of possible pancreatic RAS disorders was provided by an up-to-date access to biomedical questions, namely the study of receptors, receptor subtypes, and the gene expression of the RAS components. To better understand the contribution of these observations to possible clinical complications and, subsequently the potential

improvement of therapy, the next step of the physiological and pathophysiological approaches must first take into account the distribution and the density of receptors along vascular or other structures. Functional studies in valid experimental models should follow. A predominant location in the vascular bed must and will correspond to the results of extended microcirculatory studies. Indeed, initial measurements demonstrate vascular sensitivity in the pancreas that can be measured using intravital microscopy of the intact organ outside the animal. These measurements are to be continued with the aim of determining typical angiotensin II sensitive parts of the pancreas vasculature and their dose-response relations, before variations under the conditions of hypoxia and/or pancreatitis can be measured.

Also, the time course of the stimulus – reaction coupling of the gene expression over the regulation of protein synthesis, modifications of receptor density and cellular reaction – vasoconstriction have to be considered.

On the other hand, a localization that associates components of the RAS with different secretory functions, and associated variations in gene expression and protein synthesis, must give rise to a variety of biochemical and metabolic studies that will reveal changes in the endocrine and exocrine function.

Actual Importance of the RAS in the Clinical Setting

Up to now, only scarce information exists regarding the clinical parameters that could connect pancreatitis with RAS; a direct involvement of the RAS has neither been considered in experimental nor in clinical studies. However, pancreatitis has been described as an occasional side effect during the administration of ACE–blockers [23, 24]. For angiotensin II-type-1 antagonists there are no data available yet. As a consequence, clinical studies are being prepared.

Future Clinical Perspectives

Clinical data from patients with pancreatitis have to be evaluated with respect to components of the RAS; in particular, plasma levels of angiotensin II, angiotensinogen and renin will be of interest. Also, the incidence of different types of pancreatitis in hypertensive patients with or without specific antihypertensive therapies should be evaluated. These studies will have to take into account more than just the obvious functional parameters.

Most likely, interactions exist between those parameters that will have to be elucidated in future experimental studies. Although angiotensin II is the obvious link between RAS and the microcirculation of organs [25], there is the wide field of control of secretory activity in many cell types of various organs that is also influenced and can be impaired by malfunctions of the RAS.

As a consequence, additional steps towards a causal therapy of pancreatitis or of post-transplant complications should be developed.

Key words Renin; Renin-Angiotensin System; Microcirculation, Pancreatitis

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References

1. Guyton AC, Hall JE. Textbook of Medical Physiology. Philadelphia: WB Saunders, 2000.

2. Hackenthal E, Taugner R, Nobiling R. Intrarenal and intracellular distribution of renin and angiotensin. In: JIS Robertson JIS, Nicholls MG, Eds. The Renin-

Angiotensin System. Vol. I: Biochemistry, Physiology. Chapter 18. London (UK): Gower Medical Publishing, l993.

3. Hackenthal E. Nobiling R. Renin secretion and its regulation. In: Swales JD, Ed. Textbook of Hypertension.. Oxford (UK): Blackwell, 1994: 232-43.

4. Tigerstedt R, Bergman PG. Niere und Kreislauf. Skand Arch Physiol 1898; 8:223-71.

5. Taugner C, Poulsen K, Hackenthal E, Taugner R. Immunohistochemical localization of renin in mouse kidney. Histochemistry 1979; 62:19-27. [80006202]

6. Taugner R, Hackenthal E, Nobiling R, Harlacher M, Reb G. The distribution of renin in the different segments of the renal arterial tree. Histochemistry 1981; 73:75-88.

7. Taugner R, Bührle CP, Nobiling R. Ultrastructural changes associated with renin secretion from the juxtaglomerular apparatus of mice. Cell Tiss Res 1984; 237:459-72.

8. Taugner R, Bührle CP, Hackenthal E, Nobiling R. Typical and atypical aspects of renin secretion from juxtaglomerular epithelioid cells. Klin Wochenschr 1986; 64:829-37.

9. Bührle CP, Scholz H, Hackenthal E, Nobiling R, Taugner R. Epithelioid cells: membrane potential changes induced by substances influencing renin secretion. Mol Cell Endocrinol 1986; 45:37-47.

10. Parekh N, Dobrowolski L, Zou AP, Steinhausen M. Nitric oxide modulates angiotensin II- and norepinephrine-dependent vasoconstriction in rat kidney. Am J Physiol 1996; 270:R630-5. [96373939]

11. Skott O. Episodic release of renin from single isolated superfused rat afferent arterioles. Pflügers Archiv 1986; 407:41-5.

12. Taugner R and Hackenthal E. The Juxtaglomerular Apparatus. Berlin (D): Springer, 1989.

13. Berthold H, Munter K, Just A, Kirchheim HR, Ehmke H. Stimulation of the renin-angiotensin system by endothelin subtype A receptor blockade in conscious dogs. Hypertension 1999; 33:1420-4.

14. Nobiling R, Münter K, Bührle CP, Hackenthal E. Influence of pulsatile perfusion upon renin release from the isolated perfused rat kidney. Pflügers Archiv 1990; 415:713-7.

15. Taugner R, Mannek E, Nobiling R, Bührle CP, Hackenthal E, Ganten D, et al. Coexistence of renin and angiotensin II in epithelioid cell secretory granules of rat kidney. Histochemistry 1984; 8l:39-45.

16. Celio MR. Angiotensin II immunoreactivity coexists with renin in the juxtaglomerular granular cells of the kidney. Proc Natl Acad Sci USA 1981; 78:3897-900.

17. Nobiling R, Gabel M, Persson PB, Dietrich M, Bührle CP. Differential effect of neuropeptide-Y on membrane potential of cells in renal arterioles of the hydronephrotic mouse. J Physiol 1991; 444:317-27. [92349304]

18. Dietrich MS, Fretschner M, Nobiling R, Persson P, Steinhausen M. Renovascular effects of neuropeptide-Y in the split hydronephrotic kidney: non-uniform pattern of vascular reactivity. J Physiol 1991; 444:303-15. [92349303]

19. Zhuo J, Moeller I, Jenkins T, Chai SY, Allen AM, Ohishi M, Mendelsohn FAO. Mapping tissue angiotensin-converting enzyme and angiotensin AT_1, AT_2 and AT_4 receptors. J Hypertens 1998; 16:2027-37.

20. 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]

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

22. Foitzik T, Forgacs B, Ryschich E, Hotz H, Gebhard MM, Buhr HJ, Klar E. Effect of different immunosuppressive agents on acute pancreatitis. Transplantation 1998; 65:1030-6.

23. Marinella MA, Billi JE. Lisinopril therapy associated with acute pancreatitis. Western J Med 1995; 163:77-8.

24. Muchnick JS, Mehta JL. Angiotensin-converting enzyme inhibitor-induced pancreatitis. Clin Cardiol 1999; 22:50-1.

25. Steinhausen M, Kücherer H, Parekh N, Weis S, Wiegman DL, Wilhelm KR. Angiotensin II control of the renal microcirculation: effect of blockade by saralasin. Kidney Int 1986; 30:56-61. [86308912]