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Prorenin/renin and insulin resistance

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1. ABSTRACT

Recently we showed that fructose feeding in rats induced nonproteolytic activation of prorenin and subsequent angiotensin II production in skeletal muscle. In addition, a pharmacological inhibitor of prorenin/(pro)renin receptor interaction attenuated the development of insulin resistance. However, the inhibitor did not ameliorate the glucose intolerance in transgenic rats overexpressing the human renin gene. This review article summarizes the current knowledge of the effects of the prorenin/(pro)renin receptor system on insulin resistance and its potential as a therapeutic target.

2. PRORENIN/(PRO)RENIN RECEPTOR

(Pro)renin receptors are expressed in the kidney as well as in various other organs, including liver, pancreas, and adipose tissue (1, 2). It is believed that its physiological ligands are renin and prorenin.

Prorenin, which is known as a physiologically inactive precursor of renin, has an amino-terminal prosegment that is thought to cover its enzymatic cleft and obstruct access to its substrate, angiotensinogen. The N-terminal prosegment of human prorenin has a protruding pentameric segment known as the “handle region” and an

adjacent tetrameric segment known as the "gate region" that is not accessible by its specific monoclonal antibodies until it is loosened from the active cleft (3). When the handle region of the prorenin prosegment binds to the (pro)renin receptor, the receptor-bound prorenin changes its conformation, exposing the enzymatic cleft, and gains "renin activity" similar to that of free renin without proteolytic cleavage of its prosegment (3, 4).

The non-proteolytically activated prorenin is believed to accelerate the local production of angiotensin II (Ang II) (1). Locally produced Ang II acts as an autocrine/paracrine factor and induces local actions, which could be independent of the systemic actions induced by circulating Ang II. In addition to the Ang I generating ability, the (pro)renin receptor triggers its own intracellular signal transduction in response to (pro)renin, which is believed to be an Ang II-independent phenomenon(1, 5). The currently available pharmacological inhibitor of the prorenin/(pro)renin receptor system is a decoy peptide that is capable of competing with the handle region of prorenin for binding to its receptor and inhibiting the nonproteolytic activation (handle region decoy peptide, HRP) (6-8).

3. INSULIN RESISTANCE AND PRORENIN/(PRO)RENIN RECEPTOR

Insulin resistance is a common pathological state in which target tissues, such as muscle, adipocytes and liver, fail to respond to insulin (9). This condition occurs in a wide variety of pathological states, such as obesity, hypertension, chronic infection and cardiovascular diseases, and is a central component of type 2 diabetes mellitus (9-12).

Recent studies have suggested that upregulation of the renin-angiotensin system (RAS) impairs insulin sensitivity (10, 13), and treatment with angiotensin AT_1 receptor blockers prevents the development of insulin resistance in hypertensive patients (14-16). This indicates that Ang II contributes to the development of insulin resistance. However, the mechanisms by which RAS is activated during the development of insulin resistance are unclear because plasma renin activity and Ang II levels are often in the normal range in patients with insulin resistance. Therefore, we hypothesized that the prorenin/(pro)renin receptor system was activated in the tissues that are important for insulin action and contributed in the development of insulin resistance. We investigated this by using a fructose feeding-induced experimental model for insulin resistance in rats (17). We found that treatment with HRP markedly improved glucose intolerance assessed by an oral glucose tolerance test in high fructose-fed rats. In addition, HRP-treated rats showed a smaller increase in insulin level in response to oral glucose administration than non-treated rats, suggesting that nonproteolytic prorenin activation contributed to the fructose-induced insulin resistance. Importantly, fructose feeding stimulated nonproteolytic activation of prorenin in skeletal muscle, but not adipose tissue, and the increase in the fructose feeding-induced Ang II content in skeletal muscle was attenuated in HRP-treated rats. These findings indicate that nonproteolytic activation of prorenin participates in the development of insulin resistance through local skeletal muscle RAS activation in high fructose-fed rats, and that the (pro)renin/(pro)renin receptor/angiotensin system may be one of the therapeutical targets not only for diabetic complications (6, 18, 19), but also for insulin resistance to prevent the development of diabetes.

Prorenin is the translational product of the renin gene. Thus, if the (pro)renin/(pro)renin receptor system participates in insulin resistance like we demonstrated, one could expect that genetic manipulation of the renin gene affects insulin sensitivity. Although this is likely to be the case, the involvement of the (pro)renin/(pro)renin receptor system has yet to be cleared. Mice lacking the renin gene are lean and have high insulin sensitivity (Table 1) (20). Surprisingly, supplemental administration of Ang II abrogated the changes induced by the deletion of the renin gene. This suggests that the byproduct of renin or nonproteolytically activated prorenin, Ang II, intrinsically exaggerated the insulin sensitivity in these mice. Alternatively, that the lack of the renin gene might Ang II-independently increase insulin sensitivity in these mice by unknown mechanisms and exogenous Ang II might reduce insulin sensitivity independently from the gene knockout.

Conversely, renin transgenic animals are obese and seem to have low insulin sensitivity (Table 1) (21, 22). Human renin gene transgenic mice are obese, hyperglycemic and hyperinsulinemic with hypertrophied pancreatic islets (21), even though human renin has limited ability to enzymatically convert the mouse angiotensinogen to Ang I because of species differences (23, 24). Rat models carrying the human renin gene developed moderate obesity and glucose intolerance with greater food intake than normal Sprague Dawley control rats (22). In contrast with the results from the knockout mice, none of the angiotensin converting enzyme inhibitors (ACEI), renin inhibitor or HRP attenuated the obesity, glucose intolerance and appetite. Since both ACEI and aliskiren appear to inhibit Ang II production by (pro)renin, the result indicates that neither Ang II from renin nor from nonproteolytically activated prorenin is responsible for the metabolic changes caused by (pro)renin in human renin transgenic rats. The remaining known physiological function of (pro)renin to possibly cause the changes in renin transgenic animals is by intracellular signaling triggered by the (pro)renin/(pro)renin receptor interaction as summarized in Table 1. The transgenic rats showed a marked increase in plasma (pro)renin (25). Because either prorenin or renin triggers the intracellular signaling, the high ligand levels in the transgenic rats might induce excessive intracellular signaling and be involved in the development of obesity and glucose intolerance. HRP might not elicit its pharmacological effect due to its limited inhibitory effect on the interaction of renin/(pro)renin receptor (26) and/or its disadvantage as a decoy inhibitor on the competition with high levels of prorenin. Another possibility is that (pro)renin/(pro)renin receptor interactions in the brain could be responsible for the metabolic changes, such as increased appetite, obesity and glucose intolerance, in the transgenic animals, because both (pro)renin and (pro)renin

Table 1. Summary of phenotype change and the effect of RAS inhibitors in renin gene manipulated rodents

		Knockout	**Transgenic**			
Phenotype		**Lean, high insulin sensitivity**	**Obese, glucose intolerance**			
Product from the gene		–	Renin		Prorenin	
Action induced by the products		–	Ang I generation*	Intracellular Signal	Ang I generation*	Intracellular Signal
Inhibitory effect of blocker	ACEI	–	+[#]	–	+[#]	–
	Aliskiren	–	+	–	+	–
	HRP	–	–	–	+	+/–

The lack of renin increases insulin sensitivity, and the renin transgene results in the impaired glucose tolerance, indicating that prorenin and/or renin participates in the insulin sensitivity. If Ang II is responsible on these phenotype changes, both ACEI and aliskiren can inhibit these phenotype changes, but the drugs had no effect (22). Thus, the intracellular signaling that is likely insensitive for the drugs could be the cause of the phenotype changes.–: no effect (including no evidence), *: Ang I generating activity of human renin is limited in transgenic rodents because of high species specificity between human renin and rodent angiotensinogen, #: Inhibitory effect for the subsequent Ang II production, RAS: renin-angiotensin system, ACEI: angiotensin-converting enzyme inhibitor, HRP: handle region peptide.

receptors are found to be expressed in the brain (1, 25, 27). However, the role of the central (pro)renin/(pro)renin receptor system has not yet been clarified.

4. CONCLUSION

The (pro)renin/(pro)renin receptor system may play a role in insulin resistance. However, the physiological and pathophysiological roles of (pro)renin and its receptor in the tissues that are important for insulin action are still unclear, despite the fact that the tissues, such as liver and pancreas, highly express the (pro)renin receptor gene. Because of the phenotype changes in transgenic animals it is likely that (pro)renin is involved in the regulation of insulin sensitivity. Therefore, transgenic technology may advance the issue that we face by generating, for example, inducible tissue-targeted (pro)renin receptor transgenic or knockout animals. Furthermore, it is necessary to explore the intracellular signaling pathway triggered by (pro)renin receptor activation, and examine if it may interact with the signal induced by insulin receptor activation as is the case with angiotensin II (28) and aldosterone (29).

5. REFERENCES

1. Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD: Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 109, 1417-1427 (2002)

2. Achard V, Boullu-Ciocca S, Desbriere R, Nguyen G, Grino M: Renin receptor expression in human adipose tissue. *Am J Physiol Regul Integr Comp Physiol* 292, R274-R282 (2007)

3. Suzuki F, Hayakawa M, Nakagawa T, Nasir UM, Ebihara A, Iwasawa A, Ishida Y, Nakamura Y, Murakami K: Human prorenin has "gate and handle" regions for its non-proteolytic activation. *J Biol Chem* 278, 22217-22222 (2003)

4. Nabi AH, Kageshima A, Uddin MN, Nakagawa T, Park EY, Suzuki F: Binding properties of rat prorenin and renin to the recombinant rat renin/prorenin receptor prepared by a baculovirus expression system. *Int J Mol Med* 18, 483-488 (2006)

5. Zhang J, Noble NA, Border WA, Owens RT, Huang Y: Receptor-dependent prorenin activation and induction of PAI-1 expression in vascular smooth muscle cells. *Am J Physiol Endocrinol Metab* 295, E810-E819 (2008)

6. Ichihara A, Hayashi M, Kaneshiro Y, Suzuki F, Nakagawa T, Tada Y, Koura Y, Nishiyama A, Okada H, Uddin MN, Nabi AH, Ishida Y, Inagami T, Saruta T: Inhibition of diabetic nephropathy by a decoy peptide corresponding to the "handle" region for nonproteolytic activation of prorenin. *J Clin Invest* 114, 1128-1135 (2004)

7. Uddin MN, Nabi AH, Nakagawa T, Ichihara A, Inagami T, Suzuki F: Non-proteolytic activation of prorenin: activation by (pro)renin receptor and its inhibition by a prorenin prosegment, "decoy peptide". *Front Biosci* 13, 745-753 (2008)

8. Nurun NA, Uddin NM, Nakagawa T, Iwata H, Ichihara A, Inagami T, Suzuki F: Role of "handle" region of prorenin prosegment in the non-proteolytic activation of prorenin by binding to membrane anchored (pro)renin receptor. *Front Biosci* 12, 4810-4817 (2007)

9. Kahn SE, Hull RL, Utzschneider KM: Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 444, 840-846 (2006)

10. Sarzani R, Salvi F, Dessi-Fulgheri P, Rappelli A: Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. *J Hypertens* 26, 831-843 (2008)

11. Redon J, Cifkova R, Laurent S, Nilsson P, Narkiewicz K, Erdine S, Mancia G: Mechanisms of hypertension in the cardiometabolic syndrome. *J Hypertens* 27, 441-451 (2009)

12. Mellor KM, Ritchie RH, Delbridge LM: Reactive Oxygen Species and Insulin Resistant Cardiomyopathy. *Clin Exp Pharmacol Physiol* (2009)

13. Henriksen EJ: Improvement of insulin sensitivity by antagonism of the renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol* 293, R974-R980 (2007)

14. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg BE, Wester PO, Bjorck JE: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 353, 611-616 (1999)

15. Henriksen EJ, Jacob S, Kinnick TR, Teachey MK, Krekler M: Selective angiotensin II receptor receptor antagonism reduces insulin resistance in obese Zucker rats. *Hypertension* 38, 884-890 (2001)

16. Lindholm LH, Ibsen H, Borch-Johnsen K, Olsen MH, Wachtell K, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman JM, Snapinn S: Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens* 20, 1879-1886 (2002)

17. Nagai Y, Ichihara A, Nakano D, Kimura S, Pelisch N, Fujisawa Y, Hitomi H, Hosomi N, Kiyomoto H, Kohno M, Ito H, Nishiyama A: Possible contribution of the non-proteolytic activation of prorenin to the development of insulin resistance in fructose-fed rats. *Exp Physiol* 94, 1016-1023 (2009)

18. Satofuka S, Ichihara A, Nagai N, Noda K, Ozawa Y, Fukamizu A, Tsubota K, Itoh H, Oike Y, Ishida S: (Pro)renin receptor-mediated signal transduction and tissue renin-angiotensin system contribute to diabetes-induced retinal inflammation. *Diabetes* 58, 1625-1633 (2009)

19. Matavelli LC, Huang J, Siragy HM: (Pro)renin Receptor Contributes to Diabetic Nephropathy Through Enhancing Renal Inflammation. *Clin Exp Pharmacol Physiol* (2009)

20. Takahashi N, Li F, Hua K, Deng J, Wang CH, Bowers RR, Bartness TJ, Kim HS, Harp JB: Increased energy expenditure, dietary fat wasting, and resistance to diet-induced obesity in mice lacking renin. *Cell Metab* 6, 506-512 (2007)

21. Uehara S, Tsuchida M, Kanno T, Sasaki M, Nishikibe M, Fukamizu A: Late-onset obesity in mice transgenic for the human renin gene. *Int J Mol Med* 11, 723-727 (2003)

22. Gratze P, Boschmann M, Dechend R, Qadri F, Malchow J, Graeske S, Engeli S, Janke J, Springer J, Contrepas A, Plehm R, Klaus S, Nguyen G, Luft FC, Muller DN: Energy metabolism in human renin-gene transgenic rats: does renin contribute to obesity? *Hypertension* 53, 516-523 (2009)

23. Arakawa K, Nakatani M, Nakamura M: Species specificity in reaction between renin and angiotensinogen. *Nature* 207, 636 (1965)

24. Yang G, Merrill DC, Thompson MW, Robillard JE, Sigmund CD: Functional expression of the human angiotensinogen gene in transgenic mice. *J Biol Chem* 269, 32497-32502 (1994)

25. Ganten D, Wagner J, Zeh K, Bader M, Michel JB, Paul M, Zimmermann F, Ruf P, Hilgenfeldt U, Ganten U: Species specificity of renin kinetics in transgenic rats harboring the human renin and angiotensinogen genes. *Proc Natl Acad Sci U S A* 89, 7806-7810 (1992)

26. Nabi AH, Biswas KB, Nakagawa T, Ichihara A, Inagami T, Suzuki F: Prorenin has high affinity multiple binding sites for (pro)renin receptor. *Biochim Biophys Acta* 1794, 1838-1847 (2009)

27. McKinley MJ, Albiston AL, Allen AM, Mathai ML, May CN, McAllen RM, Oldfield BJ, Mendelsohn FA, Chai SY: The brain renin-angiotensin system: location and physiological roles. *Int J Biochem Cell Biol* 35, 901-918 (2003)

28. Velloso LA, Folli F, Sun XJ, White MF, Saad MJ, Kahn CR: Cross-talk between the insulin and angiotensin signaling systems. *Proc Natl Acad Sci U S A* 93, 12490-12495 (1996)

29. Hitomi H, Kiyomoto H, Nishiyama A, Hara T, Moriwaki K, Kaifu K, Ihara G, Fujita Y, Ugawa T, Kohno M: Aldosterone suppresses insulin signaling via the downregulation of insulin receptor substrate-1 in vascular smooth muscle cells. *Hypertension* 50, 750-755 (2007)

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