

# BÖLÜM 1



## RENİN-ANJİYOTENSİN-ALDOSTERON SİSTEMİ FİZYOLOJİSİ

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### GİRİŞ

Renin-anjiyotensin-aldosteron sistemi (RAAS), kan hacminin ve sistemik vasküler direncin kritik bir düzenleyicisidir. Bu sistemin aktivasyonu endotel disfonksiyonu, vasküler yeniden şekillenme, hipertansiyon, kalp yetmezliği ve böbrek hastalığı dahil olmak üzere birçok patolojik durumun merkezinde rol alır. Baroreseptör refleksi azalmış kan basıncına kısa süreli yanıt verirken, RAAS daha kronik değişikliklerden sorumludur. RAAS, üç ana bileşenden oluşur: renin, anjiyotensin II ve aldosteron. Bu üçü, azalan renal kan akımına, distal kıvrımlı tübüle ulaşan azalmış sodyum yüküne ve/veya beta-agonizme yanıt olarak arter basıncını yükseltmek için hareket eder. Bu mekanizmalar sayesinde vücut, kan basıncını uzun süre yükseltebilir.<sup>1,2</sup>

RAAS yolu klasik olarak böbrek jukstaglomerüler (JG) hücrelerinden salgılanan renin'in, karaciğerde üretilen ve substratı olan anjiyotensinojen'i anjiyotensin I'e dönüştürmesi ile başlar. Anjiyotensin I'in anjiyotensin II'ye dönüşümü, anjiyotensin dönüştürücü enzim (ACE) adı verilen bir enzim tarafından katalize edilir. Anjiyotensin II, böbrek üstü bezinden aldosteron salınımının yanı sıra vazokonstriksiyona aracılık eder, bu da sodyum tutulmasına ve kan basıncının artmasına neden olur. (Şekil 1)

RAAS, endokrin etkilerine ek olarak otokrin (hücreden aynı hücreye) ve parakrin (hücreden farklı hücreye) etkileri olan lokal sistemleri içerir. Anjiyotensin II kalp, böbrek, kan damarları, adrenal bez ve beyin dahil olmak üzere çeşitli doku bölgelerinde lokal olarak sentezlenebilir. Bu nedenle plazma renin aktivitesinin

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**KAYNAKLAR**

1. Liu J, Zhou Y, Liu Y, Li L, Chen Y, Liu Y, Feng Y, Yosypiv IV, Song R, Peng H. (Pro)renin receptor regulates lung development via the Wnt/ $\beta$ -catenin signaling pathway. *Am J Physiol Lung Cell Mol Physiol*. 2019 Aug 01;317(2):L202-L211.
2. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. *Nat Rev Nephrol*. 2019 Jun;15(6):367-385.
3. Sarraf M, Masoumi A, Schrier RW. Cardiorenal syndrome in acute decompensated heart failure. *Clin J Am Soc Nephrol* 2009; 4:2013.
4. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med* 2001; 345:1689.
5. Toffelmire EB, Slater K, Corvol P, et al. Response of plasma prorenin and active renin to chronic and acute alterations of renin secretion in normal humans. Studies using a direct immunoradiometric assay. *J Clin Invest* 1989; 83:679.
6. Naftilan AJ, Zuo WM, Ingelfinger J, et al. Localization and differential regulation of angiotensinogen mRNA expression in the vessel wall. *J Clin Invest* 1991; 87:1300.
7. Schunkert H, Ingelfinger JR, Hirsch AT, et al. Evidence for tissue-specific activation of renal angiotensinogen mRNA expression in chronic stable experimental heart failure. *J Clin Invest* 1992; 90:1523.
8. Shriker K, Holmer S, Krämer BK, et al. The role of angiotensin II in the feedback control of renin gene expression. *Pflügers Arch* 1997; 434:166.
9. Bock HA, Hermle M, Brunner FP, Thiel G. Pressure dependent modulation of renin release in isolated perfused glomeruli. *Kidney Int* 1992; 41:275.
10. Freeman RH, Davis JO, Villarreal D. Role of renal prostaglandins in the control of renin release. *Circ Res* 1984; 54:1.
11. Lorenz JN, Weihprecht H, Schnermann J, et al. Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. *Am J Physiol* 1991; 260:F486.
12. Fisher ND, Jan Danser AH, Nussberger J, et al. Renal and hormonal responses to direct renin inhibition with aliskiren in healthy humans. *Circulation* 2008; 117:3199.
13. Fisher ND, Hollenberg NK. Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol* 2005; 16:592.
14. Friedrich S, Schmieder RE. Review of direct renin inhibition by aliskiren. *J Renin Angiotensin Aldosterone Syst* 2013; 14:193.
15. Persson F, Rossing P, Parving HH. Direct renin inhibition in chronic kidney disease. *Br J Clin Pharmacol* 2013; 76:580.
16. Franken AA, Derckx FH, Man in't Veld AJ, et al. High plasma prorenin in diabetes mellitus and its correlation with some complications. *J Clin Endocrinol Metab* 1990; 71:1008.
17. Deinum J, Rønn B, Mathiesen E, et al. Increase in serum prorenin precedes onset of microalbuminuria in patients with insulin-dependent diabetes mellitus. *Diabetologia* 1999; 42:1006.
18. Shaw KJ, Do YS, Kjos S, et al. Human decidua is a major source of renin. *J Clin Invest* 1989; 83:2085.
19. Lumbers ER, Pringle KG. Roles of the circulating renin-angiotensin-aldosterone system in human pregnancy. *Am J Physiol Regul Integr Comp Physiol* 2014; 306:R91.
20. Nguyen G, Delarue F, Burcklé C, et al. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002; 109:1417.
21. Nguyen G, Burckle C, Sraer JD. The renin receptor: the facts, the promise and the hope. *Curr Opin Nephrol Hypertens* 2003; 12:51.
22. Price DA, Porter LE, Gordon M, et al. The paradox of the low-renin state in diabetic nephropathy. *J Am Soc Nephrol* 1999; 10:2382.
23. Nguyen G. Renin, (pro)renin and receptor: an update. *Clin Sci (Lond)* 2011; 120:169.
24. Liu J, Zhou Y, Liu Y, et al. (Pro)renin receptor regulates lung development via the Wnt/ $\beta$ -catenin signaling pathway. *Am J Physiol Lung Cell Mol Physiol* 2019; 317:L202.
25. Corvol P, Jeunemaitre X. Molecular genetics of human hypertension: role of angiotensinogen. *Endocr Rev* 1997; 18:662.

26. Koizumi M, Niimura F, Fukagawa M, Matsusaka T. Adipocytes do not significantly contribute to plasma angiotensinogen. *J Renin Angiotensin Aldosterone Syst* 2016; 17:1470320316672348.
27. Schunkert H, Danser AH, Hense HW, et al. Effects of estrogen replacement therapy on the renin-angiotensin system in postmenopausal women. *Circulation* 1997; 95:39.
28. Gürdal F, Ademoğlu E. *Biyokimya, Nobel Kitap Evi*, 2005: 746-747.
29. Dzau VJ, Bernstein K, Celermajer D, et al. Pathophysiologic and therapeutic importance of tissue ACE: a consensus report. *Cardiovasc Drugs Ther* 2002; 16:149.
30. Ondetti MA, Rubin B, Cushman DW. Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science* 1977; 196:441.
31. Izzo JL Jr, Weir MR. Angiotensin-converting enzyme inhibitors. *J Clin Hypertens (Greenwich)* 2011; 13:667.
32. Weir MR, Henrich WL. Theoretical basis and clinical evidence for differential effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor subtype 1 blockers. *Curr Opin Nephrol Hypertens* 2000; 9:403.
33. Donoghue M, Hsieh F, Baronas E, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res* 2000; 87:E1.
34. Vickers C, Hales P, Kaushik V, et al. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. *J Biol Chem* 2002; 277:14838.
35. Santos RA, Simoes e Silva AC, Maric C, et al. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proc Natl Acad Sci U S A* 2003; 100:8258.
36. Ichikawa I, Harris RC. Angiotensin actions in the kidney: renewed insight into the old hormone. *Kidney Int* 1991; 40:583.
37. Yuan BH, Robinette JB, Conger JD. Effect of angiotensin II and norepinephrine on isolated rat afferent and efferent arterioles. *Am J Physiol* 1990; 258:F741.
38. Dandona P, Dhindsa S, Ghanim H, Chaudhuri A. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. *J Hum Hypertens* 2007; 21:20.
39. Ruiz-Ortega M, Lorenzo O, Rupérez M, et al. Angiotensin II activates nuclear transcription factor kappaB through AT(1) and AT(2) in vascular smooth muscle cells: molecular mechanisms. *Circ Res* 2000; 86:1266.
40. Pueyo ME, Gonzalez W, Nicoletti A, et al. Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor-kappaB activation induced by intracellular oxidative stress. *Arterioscler Thromb Vasc Biol* 2000; 20:645.
41. Kranzhöfer R, Browatzki M, Schmidt J, Kübler W. Angiotensin II activates the proinflammatory transcription factor nuclear factor-kappaB in human monocytes. *Biochem Biophys Res Commun* 1999; 257:826.
42. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996; 334:1649.
43. Romero CA, Orias M, Weir MR. Novel RAAS agonists and antagonists: clinical applications and controversies. *Nat Rev Endocrinol* 2015; 11:242.
44. Carey RM. The intrarenal renin-angiotensin and dopaminergic systems: control of renal sodium excretion and blood pressure. *Hypertension* 2013; 61:673.
45. Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: Physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. *Pharmacol Res* 2017; 125:21.
46. Santos RAS, Oudit GY, Verano-Braga T, et al. The renin-angiotensin system: going beyond the classical paradigms. *Am J Physiol Heart Circ Physiol* 2019; 316:H958.
47. Kakiki M, Morohashi K, Nomura M, et al. Expression of aldosterone synthase cytochrome P450 (P450aldo) mRNA in rat adrenal glomerulosa cells by angiotensin II type 1 receptor. *Endocr Res* 1997; 23:277.
48. Kifor I, Moore TJ, Fallo F, et al. Potassium-stimulated angiotensin release from superfused adrenal capsules and enzymatically dispersed cells of the zona glomerulosa. *Endocrinology* 1991; 129:823.

49. Jaisser F, Farman N. Emerging Roles of the Mineralocorticoid Receptor in Pathology: Toward New Paradigms in Clinical Pharmacology. *Pharmacol Rev* 2016; 68:49.
50. Sztzechman D, Czarzasta K, Cudnoch-Jedrzejska A, et al. Aldosterone and mineralocorticoid receptors in regulation of the cardiovascular system and pathological remodelling of the heart and arteries. *J Physiol Pharmacol* 2018; 69.
51. Takeda Y, Miyamori I, Yoneda T, et al. Regulation of aldosterone synthase in human vascular endothelial cells by angiotensin II and adrenocorticotropin. *J Clin Endocrinol Metab* 1996; 81:2797.
52. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991; 83:1849.
53. Young M, Fullerton M, Dilley R, Funder J. Mineralocorticoids, hypertension, and cardiac fibrosis. *J Clin Invest* 1994; 93:2578.
54. Chun TY, Bloem LJ, Pratt JH. Aldosterone inhibits inducible nitric oxide synthase in neonatal rat cardiomyocytes. *Endocrinology* 2003; 144:1712.
55. O'Neil RG, Hayhurst RA. Sodium-dependent modulation of the renal Na-K-ATPase: influence of mineralocorticoids on the cortical collecting duct. *J Membr Biol* 1985; 85:169.
56. Guo C, Ricchiuti V, Lian BQ, et al. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation* 2008; 117:2253.
57. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. *Curr Hypertens Rep* 2013; 15:59.
58. Garg R, Adler GK. Aldosterone and the Mineralocorticoid Receptor: Risk Factors for Cardiometabolic Disorders. *Curr Hypertens Rep* 2015; 17:52.
59. Buglioni A, Cannone V, Cataliotti A, et al. Circulating aldosterone and natriuretic peptides in the general community: relationship to cardiorenal and metabolic disease. *Hypertension* 2015; 65:45.
60. Hanslik G, Wallaschofski H, Dietz A, et al. Increased prevalence of diabetes mellitus and the metabolic syndrome in patients with primary aldosteronism of the German Conn's Registry. *Eur J Endocrinol* 2015; 173:665.
61. Wagner C, Jensen BL, Kramer BK, Kurtz A. Control of the renal renin system by local factors. *Kidney Int* 1998; 54 (suppl 67):S78.
62. Dzau VJ. Tissue renin-angiotensin system in myocardial hypertrophy and failure. *Arch Intern Med* 1993; 153:937.
63. Ren L, Lu X, Danser AHJ. Revisiting the Brain Renin-Angiotensin System-Focus on Novel Therapies. *Curr Hypertens Rep* 2019; 21:28.
64. Wilkes BM, Mento PF, Pearl AR, et al. Plasma angiotensins in anephric humans: evidence for an extrarenal angiotensin system. *J Cardiovasc Pharmacol* 1991; 17:419.
65. Paul M, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev* 2006; 86:747.
66. Matsusaka T, Niimura F, Shimizu A, et al. Liver angiotensinogen is the primary source of renal angiotensin II. *J Am Soc Nephrol* 2012; 23:1181.
67. Carey RM, Siragy HM. Newly recognized components of the renin-angiotensin system: potential roles in cardiovascular and renal regulation. *Endocr Rev* 2003; 24:261.
68. Yang T, Xu C. Physiology and Pathophysiology of the Intrarenal Renin-Angiotensin System: An Update. *J Am Soc Nephrol* 2017; 28:1040.
69. Ingelfinger JR, Zuo WM, Fon EA, et al. In situ hybridization evidence for angiotensinogen messenger RNA in the rat proximal tubule. An hypothesis for the intrarenal renin angiotensin system. *J Clin Invest* 1990; 85:417.
70. Yanagawa N. Potential role of local luminal angiotensin II in proximal tubule sodium transport. *Kidney Int* 1991; 39 (suppl 32):S.
71. Seikaly MG, Arant BS Jr, Seney FD Jr. Endogenous angiotensin concentrations in specific intrarenal fluid compartments of the rat. *J Clin Invest* 1990; 86:1352.

72. Siragy HM, Howell NL, Ragsdale NV, Carey RM. Renal interstitial fluid angiotensin. Modulation by anesthesia, epinephrine, sodium depletion, and renin inhibition. *Hypertension* 1995; 25:1021.
73. Wenting GJ, de Bruyn JH, Man in't Veld AJ, et al. Hemodynamic effects of captopril in essential hypertension, renovascular hypertension and cardiac failure: correlations with short- and long-term effects on plasma renin. *Am J Cardiol* 1982; 49:1453.
74. Giani JF, Shah KH, Khan Z, et al. The intrarenal generation of angiotensin II is required for experimental hypertension. *Curr Opin Pharmacol* 2015; 21:73.
75. Carey RM. The intrarenal renin-angiotensin system in hypertension. *Adv Chronic Kidney Dis* 2015; 22:204.
76. Kessler SP, deS Senanayake P, Scheidemantel TS, et al. Maintenance of normal blood pressure and renal functions are independent effects of angiotensin-converting enzyme. *J Biol Chem* 2003; 278:21105.
77. Aroor AR, Demarco VG, Jia G, et al. The role of tissue Renin-Angiotensin-aldosterone system in the development of endothelial dysfunction and arterial stiffness. *Front Endocrinol (Lausanne)* 2013; 4:161.
78. De Mello WC, Frohlich ED. On the local cardiac renin angiotensin system. Basic and clinical implications. *Peptides* 2011; 32:1774.
79. McKinley MJ, Albiston AL, Allen AM, et al. The brain renin-angiotensin system: location and physiological roles. *Int J Biochem Cell Biol* 2003; 35:901.