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肾素 - 血管紧张素 - 醛固酮系统阻滞的研究进展 *

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摘要：肾素 - 血管紧张素 - 醛固酮系统起初被认为是较简单的神经体液调节机制之一。但是，这一想法随着 RAAS 阻滞剂：肾素阻滞剂、血管紧张素转换酶抑制剂(ACEI)、AT1 受体拮抗剂及盐皮质激素受体拮抗剂的深入研究而受到挑战。因此，RAAS 的组成、以上药物发挥作用的具体通路及副作用均得到重新定义。在 RAAS 阻滞剂的应用过程中，机体肾素水平升高，并刺激肾素原受体（即无活性的肾素前体，PRR），进而对机体造成不良影响。同理，在 AT1 受体拮抗剂的应用过程中，血浆血管紧张素 II 的水平升高，并与 2 型血管紧张素 II（AT2）受体结合，进而对机体产生有利作用。此外，随着 ACEI 及 ARB 的应用，血管紧张素 1-7 水平升高，其与 Mas 受体结合，发挥心脏及肾脏保护的作用，还可通过刺激干细胞发挥组织修复作用。

关键词：肾素 - 血管紧张素 - 醛固酮系统；肾素原受体；2 型血管紧张素 II 受体；血管紧张素 1-7

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Key Developments in Renin-Angiotensin-Aldosterone System Inhibition*

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ABSTRACT: The renin-angiotensin-aldosterone system (RAAS) was initially thought to be fairly simple. However, this idea has been challenged following the development of RAAS blockers, including renin inhibitors, angiotensin-converting-enzyme (ACE) inhibitors, type 1 angiotensin II (AT1)-receptor blockers and mineralocorticoid-receptor antagonists. Consequently, new RAAS components and pathways that might contribute to the effectiveness of these drugs and/or their adverse effects have been identified. An increase in renin levels during RAAS blockade might result in harmful effects via stimulation of the prorenin receptor (PRR, the inactive precursor of rennin). The increase in angiotensin II levels that occurs during AT1-receptor blockade might result in beneficial effects via stimulation of type 2 angiotensin II (AT2) receptors. Moreover, angiotensin 1-7 levels increase during ACE inhibition and AT1-receptor blockade, resulting in Mas receptor activation and the induction of cardioprotective and renoprotective effects, including stimulation of tissue repair by stem cells.

Key words: Renin-angiotensin-aldosterone system; Prorenin receptor; Type 2 angiotensin II receptor; Angiotensin 1-7

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在过去的几十年中，人们对肾素 - 血管紧张素 - 醛固酮系统（RAAS）阻滞剂的研究不断深入，对 RAAS 系统的认识也有所更新。目前，RAAS 的阻滞剂主要包括：直接肾素阻滞剂、血管紧张素转换酶抑制剂（ACEI）、1 型血管紧张素 II 受体拮抗剂（ARB）及盐皮质激素受体拮抗剂（MRAs）虽然这些药物经常被用于治疗心血管疾病及肾脏疾病[1]，但是，事实证明它们并非像人们想象的那样能够彻底阻滞血管紧张素 II 和醛固酮的水平及其活性，甚至可能造成其水平的反弹[2]。这一现象说明，这些药物发挥对机体有利的作用机制时，并不一定只是通过对血管紧张素 II-AT1 受体 - 醛固酮这一作用通路而发挥作用，还可能存在其他作用通路。研究证明，AT1 受体阻滞剂的使用可导致机体血管紧张素 II 水平升高，增强 AT2 受体的活性，产生与 AT1 受体激活相反的作用：血管扩张、抑制心肌重塑、拮抗交感神经活性及钠水重吸收[3,4]。另外，ACEI 及 ARB 的应用可使血管紧张素 II 代谢产物增多，其中较为重要的是血管紧张素 1-7 片段，它可与 Mas 受体结合，发挥心脏及肾脏保护作用[5]。这篇综述中，我们主要着眼于肾脏，介绍 PRR 阻滞剂、AT2 受体阻滞剂和 Mas 受体阻滞剂对 RAAS 的具体作用及其心肾保护作用。

1 PRR 与 RAAS 阻滞剂

RAAS 阻滞剂可诱导糖尿病大鼠肾脏 PRR 的表达[6]，但是在高浓度血管紧张素 II 致高血压的大鼠模型研究中发现，PRR 的表达与肾素水平的升高呈平行关系[7]。无论在肾脏大部分切除（5/6 外科切除）的大鼠亦或终末期糖尿病肾病患者的研究发现，肾脏 PRR 的表达（主要是肾小管细胞及集合管）均上调[8,9]。以上研究表明，PRR 的表达可能还存在其他独立于 RAAS 系统之外的调节通路，例如：通过 NADPH 氧化活性通路发挥作

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用[6]。

尽管有以上研究结果，但我们还是不能明确肾素原-PRR反应是否存在于体内。重要的是，PRR与肾素及肾素原的结合要求其浓度在纳摩尔范围（对肾素浓度要求为20 nmol/L），当肾素及肾素原细胞外液浓度在皮摩尔时很难与PRR结合[10]。这一现象也证明PRR过度表达并不能够改变RAAS各组分的水平[11]。大部分体外研究均发现，肾素原及PRR反应可以发生，但要求肾素原达到纳摩尔浓度水平，这需要通过激活ERK1/2及纤维化基因上调才能完成[12]。而且，在肾素原高表达的啮齿类动物中，血浆肾素原的水平升高超过400倍，血压升高，但并不能出现在体研究时发现的纤维化及肾小球硬化作用[12]，说明这一作用可能要求更高的肾素原水平。而在病理状态下或应用RAAS阻滞剂的情况下，肾素原及肾素升高不会超过基线水平的三倍。目前，人体血浆中最高肾素原水平已有证实，在严重心力衰竭或RAAS阻滞剂应用时，肾素水平是正常的50-100倍，而肾素原是正常的2-3倍[2,13]。然而，在肾素原合成组织（肾间质液）中是否存在如此高浓度的肾素原及肾素水平目前尚无研究证实。

由于血管紧张素II和肾素之间的负反馈环路，当RAAS阻滞达到最大时，血浆肾素水平亦达到高峰。因此，双重或三重RAAS阻滞剂所致血浆肾素水平的增加要高于单种RAAS阻滞剂使用时的血浆肾素浓度[14]。自发性高血压大鼠给予低盐饮食后，应用双重RAAS阻滞剂可明显增加血浆及肾脏的肾素水平，并降低血管紧张素原的浓度[14]，此时，血压明显下降，但肾功能恶化。

2 AT2受体与RAAS阻滞剂

在次全肾切除的大鼠研究中，单纯使用PD123319（AT2受体阻滞剂）或同时联合ARB治疗，可降低蛋白尿及血液单核细胞，并可抑制巨噬细胞深入残余肾[15]。同理，对单侧输尿管梗阻所致肾损伤模型小鼠应用AT1受体拮抗剂（PD123319）和AT2受体拮抗剂（氯沙坦），可以保护其NFkB通路活性[16]。在大鼠的研究中发现，注射血管紧张素II可引起肾小球内单核细胞和巨噬细胞的浸润，这一过程依赖于AT2受体介导的趋化诱导[17]。在大鼠肾隔离所致高血压模型中，血管紧张素II与AT2受体相互作用可增加肾间质缓激肽水平，并激活具有保护作用的NO/cGMP通路[18]。但是，对肾切除的大鼠应用PD123319治疗可增加肾脏损伤及升高血压，这可能是由于AT2受体介导的血管扩张作用被阻滞，因此增加了残余组织的缺血性损害[19]。此外，单纯刺激AT2受体可减少自发性高血压大鼠单核细胞和巨噬细胞在大动脉和肾脏中的浸润[20]。

3 ACE2---血管紧张素1-7---Mas受体轴

ACE的同系物ACE2切割血管紧张素II生成血管紧张素1-7，可拮抗AT1受体介导的生物作用，这是通过Mas受体完成的[5]。此外，血管紧张素1-7还可由血管紧张素I生成[21]。有研究发现，血管紧张素1-7可与AT2受体结合，当血管紧张素1-7浓度较高时还可刺激AT1受体[22]。ACE2和Mas受体在肾脏、心脏、血管组织表达，这说明血管紧张素1-7对这些器官具有生理性的保护作用[23]。在心脏缺血合并心力衰竭的啮齿类动物模型中，注射血管紧张素1-7或ACE2过度表达均可产生心脏和内皮细胞保护作用，在高血压合并糖尿病模型中，这一治疗可保护肾脏，抑制心血管恶化[23,24]。在自发性高血压大鼠模型中，应用Mas受体阻滞剂：A779，可抑制ACEI的抗高血压和抗蛋白尿的作用，这说明ACEI发挥作用是依赖，或至少部分依赖Mas受体的活性[25,26]。Mas受体激活可增加内皮NO的释放，并减少氧化应激反应，从而对抗血管紧张素II的氧化作用，进而发挥抗心肌肥厚、抗纤维化及肾脏保护作用[27]。但是令人疑惑的是，将Mas受体转基因至鼠的肾小管上皮细胞，可减少血管紧张素II刺激的TGF-β1的表达，然而，在人的肾小球系膜细胞中，血管紧张素1-7刺激TGF-β1依赖的纤维化途径，这一作用可被A779阻滞[28,29]。这一现象可能是由于Mas-AT1受体的异源二聚体的存在所致，尽管存在AT2受体介导作用。

(1)对干细胞的调节作用

骨髓中的造血干细胞和骨髓间质干细胞可分化为心血管细胞（HSCs）和肾祖母细胞（MSCs），其在组织修复中起主要作用。重要的是，临床研究表明，心脏自体骨髓干细胞移植可改善缺血性心脏病患者的心功能，这主要是因为其促进血管生成[30]。与之相似，静脉注射MSC可改善慢性肾脏疾病患者的肾功能[31]。因为RAAS主要组成原件在均存在于骨髓[32]，所以RAAS系统被认为在HSC和MSC调节中起到重要作用。对放疗或化疗后的小鼠给予血管紧张素1-7，可刺激骨髓再生[33]。另一鼠类研究表明，血管紧张素1-7-Mas受体通路可刺激骨髓细胞形成早期内皮祖细胞[34]，而且，刺激骨髓Mas受体增加骨髓干细胞生成，进而成为改善组织修复的一种新方法。

(2)新兴的治疗方法

在体内，血管紧张素1-7片段很快被降解，因此一种新兴的治疗方法出现：刺激ACE2--血管紧张素1-7--Mas受体轴。羟基丙β-环糊精对血管紧张素1-7具有保护作用，其可防止血管紧张素1-7在在经过胃肠道时被降解，因此，有研究将血管紧张素1-7降入含羟基丙β-环糊精成分的胶囊内，以口服方式送入心肌梗死的大鼠体内，发现其具有心脏保护作用[35]，循环中的血管紧张素1-7以及其含硫醚桥的类似物均可抵制代谢降解，并可通过口服或呼吸道给药方式吸收入体内[36]。有意思的是，循环的血管紧张素1-7可选择性的激活Mas受体，改善心肌梗死后的心肌重塑和内皮功能[37]，而这一过程可不经过AT1或AT2受体[38]。还有研究发现，对已应用NO合酶阻滞剂的自发性高血压大鼠，给予非肽类血管紧张素1-7：AVE0991，可防止外周器官的损害[26]，还可增强乙酰胆碱诱导的血管舒张[39]。此外，ACE2激活剂XNT可改善糖尿病大鼠及自发性高血压大鼠的心功能，降低心、肾及肺的纤维化[40,41]。

PRR起初被认为是肾素原组织激活的关键受体，但是今年来研究表明，PRR还有另外的非常重要的作用。虽然敲除PRR对机体有致命性损伤，但是PRR阻滞剂是否可用于治疗仍存在争议。同样，AT2受体的功能研究表明，在AT2受体激动剂应用于临床之前，还需要进一步明确其为什么会与年龄、疾病有关。令人信服的研究表明，Mas受体具有激活干细胞修复组织损害的作用，因此，我们需要一种稳定的Mas受体激活剂或ACE2激活剂，还需进一步解决血管紧张素1-7在体内迅速降

解这一问题。

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