心血管衰老机制研究进展（二）专题

·综 述·

心血管衰老与神经激素信号失调

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摘要：神经激素信号是心血管衰老主要机制之一，其具体包括肾素 - 血管紧张素 - 醛固酮系统、β- 肾上腺素能信号及胰岛素样生长因子 -1。神经激素信号除参与心血管衰老外，还与高血压（hypertension）、心房颤动（atrial fibrillation）及心力衰竭（heart failure）等多种心血管疾病相关，两者可能存在共同机制。该文简要综述神经激素信号在心血管衰老中的作用，以期为今后心血管疾病的诊断、治疗及新药研发提供参考。

关键词：心血管系统；衰老；神经激素信号
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Cardiovascular aging and dysregulation of neurohormone signaling

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Abstract: Neurohormonal signaling is one of the main mechanisms of cardiovascular aging, which specifically includes the renin-angiotensin-aldosterone system, β-adrenergic signaling, and insulin-like growth factor-1. Neurohormonal signals are not only involved in cardiovascular failure, but also associated with various cardiovascular diseases such as hypertension, atrial fibrillation, and heart failure, and there may be a common mechanism between the two. This article reviewed the role of neurohormone signaling in cardiovascular aging, aiming to provide reference for the diagnosis, treatment, and new drugs for cardiovascular diseases in the future.

Key words: cardiovascular system; aging; neurohormonal signal

神经激素信号包括肾素 - 血管紧张素 - 醛固酮系统（renin angiotensin aldosterone system，RAAS）、β- 肾上腺素能信号和胰岛素样生长因子（insulin-like growth factor，IGF）-1 信号，在衰老过程中其被缓慢激活，从而导致心血管系统功能失调。RAAS 的激活与各类心血管疾病密切相关，包括高血压（hypertension）、动脉粥样硬化（atherosclerosis）、冠状动脉粥样硬化性心脏病（coronary atherosclerotic heart disease）、心房颤动（atrial fibrillation）和心力衰竭（heart failure，HF）[1]。故血管紧张素转换酶（angiotensin converting enzyme，ACE）抑制剂、血管紧张素（angiotensin，Ang）受体阻断剂及盐皮质激素受体拮抗剂等可作用于 RAAS 的药物被广泛用于治疗心血管疾病。本文就 RAAS、β- 肾上腺素能信号和 IGF-1 等神经激素信号在心血管衰老中的作用作简要综述，以期为今后心血管疾病的诊断、治

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疗及新药研发提供参考。

1 RAAS

激活 RAAS 会通过多种机制对心血管系统产生不利影响，包括钠稳态受损、血管张力和血容量调节不适应以及心血管系统细胞的异常生长和增殖、氧化应激、炎症和纤维化[2—3]。动物试验显示，肾素及 Ang Ⅱ循环水平呈年龄依赖性升高[4]，且老年小鼠心脏及血管中 Ang Ⅱ信使 RNA 及其蛋白表达水平亦有所增加[4—5]。Ang Ⅱ水平升高伴随着血管中 ACE、Ⅳ型胶原、纤连蛋白及转化生长因子 -β 的表达增加[4]，且老年小鼠对 Ang Ⅱ刺激更为敏感，更易发展为高血压[6]。这些研究表明，RAAS 过度激活与衰老及心血管疾病均相关。

在小鼠模型中，Ang Ⅱ受体 1A 基因突变会导致心脏纤维化及舒张功能障碍，并伴有中度高血压[7]。而大鼠模型表明，RAAS 激活与高血压、心肌肥大、心肌纤维化和舒张功能障碍密切相关，给予盐皮质激素受体拮抗剂可改善心脏舒张功能[8]。多项研究表明，针对 RAAS 信号的各类干预手段均能改善与年龄相关的心血管系统结构及功能改变，如心血管重塑、心肌增厚及心血管张力不足等[9—11]。从一定程度上可验证 RAAS 参与心血管衰老过程。值得注意的是，尽管 RAAS 抑制剂在临床上被广泛用于治疗心血管疾病，但其是否在心血管系统中具有抗衰老作用尚待阐明，而 RAAS 非经典途径中的部分肽类，如 Ang(1-7)、Ang(1-9) 及 alamandine 等对心血管系统具有保护作用[12]。

2 β- 肾上腺素能信号

β- 肾上腺素能信号在心血管疾病及衰老过程中均具有重要作用[13—14]。在 HF 患者中儿茶酚胺循环水平常升高、β- 肾上腺素能反应性降低，在老年人中同样存在类似现象[15]，且 β- 肾上腺素能受体对心肌收缩力的促进能力随年龄增长而下降[16]。虽有证据表明，通过促 β- 肾上腺素能受体过表达可激活 β- 肾上腺素能信号转导，改善心肌收缩功能，但这一改善作用仅局限于早期[17—18]，后期仍会加速心肌肥大及纤维化，最终导致心脏失代偿[17,19—21]。

现有临床研究表明，β 受体阻断剂能改善 HF 患者预后，减缓射血分数下降速度[22]，并延缓动脉粥样硬化进展[23]。与之类似，敲除小鼠腺苷酸环化酶（adenylate cyclase，Adcy）5 基因可使 β- 肾上腺素能信号失活，从而预防年龄相关的心肌肥大、收缩功能障碍、细胞凋亡及纤维化，进而延长小鼠寿命，推测可能是通过上调超氧化物歧化酶、减少线粒体活性氧、防止氧化应激实现上述作用[24]。

近来有研究表明，上调桥连整合因子（bridge integration factor，BIN）1 或能通过 β- 肾上腺素能信号转导参与衰老过程，敲除老年小鼠 *BIN1* 可改善心脏 β- 肾上腺素能反应[25]。但现有证据仍无法证实应用 β 受体阻断剂是否能通过抑制 BIN1 纠正 β- 肾上腺素能信号紊乱[26—27]。今后可进一步探索微调 β- 肾上腺素能信号在老年人心血管风险管理中的作用效果。

3 IGF-1

研究显示，IGF-1 水平随年龄增长而下降[28]，抑制生长激素 -IGF-1 轴信号转导可延长寿命[29—30]。IGF-1 信号转导对心血管健康的影响具有年龄依赖性[31]。动物试验表明，在年轻小鼠中，心肌细胞特异性过表达 IGF-1 受体（IGF-1 receptor，IGF-1R）能改善心脏功能及结构[31—32]，但在老年小鼠中心肌细胞 IGF-1 或 IGF-1R 过表达则会加重心血管衰老，缩短模型动物寿命[31,33]。分析其具体机制，与线粒体功能障碍、氧化代谢减少及心肌巨自噬丧失有关[31]。

心脏 IGF-1R 表达水平随年龄增长而升高[31,34]，心肌细胞特异性 *IGF-1R* 敲除小鼠心肌肥大、纤维化改善，促炎细胞因子水平降低[34]。给予雌性小鼠 IGF-1R 单克隆抗体可改善心功能，延长模型动物寿命[35]。此外，在磷脂酰肌醇 3- 激酶（phosphatidylinositol 3-kinase，PI3K）显性阴性雄性

小鼠中，抑制心脏 IGF-1R 信号转导可改善年龄相关的心血管衰老，延长模型动物寿命[31,36]。阿培利司（alpelisib）是一种小分子 PI3K 抑制剂，动物试验表明，其可延长小鼠中位及最长寿命[37]，但是否能延缓心血管衰老尚有待探究。

在心脏方面，研究表明，缺血性心肌病及射血分数保留的 HF 患者心肌 IGF-1R 信使 RNA 过表达[38]。但关于 IGF-1 水平与 HF 及死亡之间的具体关系现有研究结果并不一致[39—43]。这加大了以 IGF-1 信号为靶点的新疗法研发难度。故今后需进一步开展相关研究，以明确 IGF-1、IGF-1R 在心血管系统中的作用特征，从而设计具有针对性的心血管疾病治疗新方法。

在血管方面，IGF-1 循环水平下降与健康老年人脑血流量减少及神经血管偶联反应受损相关[44]；类风湿性关节炎（rheumatoid arthritis）女性患者低血清 IGF-1 水平与心血管事件发生风险增加有关[45]。此外，动物试验表明，IGF-1 水平降低会加重血管硬化及内皮功能障碍[46—47]。可见 IGF-1 减少会促进血管衰老进程，但与在心脏中观察到的现象相似，过高或过低的 IGF-1 水平均与血管意外事件的发生风险增加有关[42]。敲低小鼠 *IGF-1R* 可改善血管功能[48—49]，但所用小鼠并非老年小鼠，故这一作用是否在老年小鼠中同样存在尚有待证实。今后需开展长期研究，以阐明 IGF-1 水平在血管疾病中的具体意义，为相关疾病的诊疗提供更多靶点。

4 结语

神经激素信号在衰老过程中具有重要作用。其中 RAAS 已明确与多种心血管疾病密切相关。虽然 RAAS 抑制剂已被广泛用于治疗心血管疾病，但其心血管抗衰老作用仍待明确。β 受体阻断剂可通过抑制 β- 肾上腺素能信号改善年龄相关的心脏结构及功能异常，微调 β- 肾上腺素能信号或是老年人心血管风险管理的新方向。虽然已知 IGF-1 在心血管衰老中具有重要作用，但其在心血管系统中的作用特征仍不明确，故以 IGF-1 为靶点的新疗法研发存在较大困难，目前亟需开展更多研究来明确 IGF-1 的具体作用特征，以提供更多治疗靶点。

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