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影响醛固酮水平升高的相关因素研究进展

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摘　要

醛固酮是肾素－血管紧张素－醛固酮系统(RAAS)的一员，是参与调节水、电解质和血压稳态的主要盐皮质激素。醛固酮合成和分泌的调节主要受到促肾上腺皮质激素、循环钾浓度和血管紧张素II等刺激物的影响。近年来，大量研究已表明醛固酮作为体内的重要激素之一，醛固酮的过度分泌或调节失调在高血压、糖尿病、肥胖、肾病及心血管疾病的发生和发展中起重要作用。因此，早期认识醛固酮水平升高的相关因素及控制醛固酮水平可能是醛固酮介导的一系列疾病的预防和控制的一个环节。然而，醛固酮水平升高的影响或调节因素中，有些因素尚不够清楚或存在争议。在这篇综述中我们将总结影响醛固酮水平升高的相关因素。

关键词

醛固酮，肥胖，吸烟，饮酒，血脂，血糖，抑郁，焦虑

Research Progress on Related Factors Affecting Elevated Aldosterone Levels

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Abstract

Aldosterone is a member of the renin-angiotensin-aldosterone system (RAAS) and is the major mineralocorticoid involved in the regulation of water, electrolytes and blood pressure homeosta-

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sis. The regulation of aldosterone synthesis and secretion is mainly influenced by stimulants such as corticotropin, circulating potassium concentrations, and angiotensin II. In recent years, a lot of studies have shown that aldosterone is one of the important hormones in the body, and the excessive secretion or dysregulation of aldosterone plays an important role in the occurrence and development of hypertension, diabetes, obesity, kidney disease and cardiovascular diseases. Therefore, an early understanding of the factors associated with elevated aldosterone levels and the control of aldosterone levels may be a link in the prevention and control of a range of aldosterone-mediated diseases. However, some of the effects or regulators of aldosterone levels are not clear enough or controversial. In this review, we will summarize the influencing factors and regulators of elevated aldosterone levels.

Keywords

Aldosterone, Obesity, Smoking, Alcohol Consumption, Blood Lipids, Blood Sugar, Depression, Anxiety

1. 引言

肾素－血管紧张素－醛固酮系统(renin-angiotensin-aldosterone system, RAAS)主要由肾素、血管紧张素 I (Ang I)、血管紧张素 II (Ang II)、血管紧张素转换酶、醛固酮等构成[1]。醛固酮是 RAAS 的终产物，是一种类固醇激素，在调节电解质平衡和血压方面起着关键作用，其正常的生理调节因子包括 Ang II、K+和 ACTH，它们可以通过增加 StAR 表达和磷酸化来增加醛固酮分泌，同时也可以通过增加醛固酮合成酶(CYP11B2)基因表达来作用于激素生成途径，从而增加醛固酮分泌[2]。

近年来，醛固酮作为糖尿病、心血管疾病、高血压、肾脏疾病和肥胖等多种疾病的致病因子而受到广泛关注[3]。醛固酮升高可引起中度至重度血压升高，导致包括心血管在内的多种靶器官受损[4] [5]。基于患者和人群的观察性研究表明，循环醛固酮的升高增加了各种人群中心血管疾病发病率和死亡率的风险[6] [7] [8]。动物研究表明，醛固酮通过诱导氧化应激、炎症、肥厚性重塑、纤维化和内皮功能障碍直接影响血管系统[9] [10] [11]。此外，醛固酮和盐皮质激素受体的激活也被证明有助于慢性肾病(CKD)的发展或进展[12]。矿皮质激素受体拮抗剂(MRAs)靶向醛固酮发挥抗炎和抗纤维化作用，并提供心－肾保护，包括对高血压、心力衰竭和 CKD 的有益作用[13] [14]。因此，醛固酮的检测和早期控制醛固酮水平的升高可能是心血管预防的一个重要环节。

既往的一些研究已表明醛固酮水平相关的影响因素及其中的潜在机制。例如，一项基于人群的研究报告称，血糖、血压(BP)、体重指数(BMI)、吸烟状况和总胆固醇与循环醛固酮浓度升高有关[15]。有证据还表明，在肾素或皮质醇浓度没有变化的情况下，抑郁或焦虑症与醛固酮升高有关[16]。但有些因素及机制尚不清楚且存在争议，在这篇综述中总结目前已发现的醛固酮水平相关的影响因素及其中的机制。

2. 年龄因素

目前有不少年龄与醛固酮相关的研究。相对较小样本量的人类研究先前表明，年龄越大可能与醛固酮分泌减少有关[17]。另一项病理组织学及临床研究中已表明随着年龄的增长，正常醛固酮水平呈渐进式

下降。在这项研究中还解释了其中的机制，老年人肾上腺小球带 CYP11B2 表达较不正常，表达 CYP11B2 的细胞异常灶含量较高。CYP11B2 的表达模式随着年龄的增长而显著变化，肾素和醛固酮的生理变化也与年龄相关。

这解释了肾素不依赖型醛固酮增多症和醛固酮生理失调在老年人中普遍存在的潜在原因。此外，研究结果更好地理解了与年龄相关的醛固酮的生理作用，并为与年龄相关的心血管风险提供了潜在的解释[18]。既往的研究需进一步探索可能对老年人的高血压及心血管疾病的预防和控制带来收益。

3. 性别因素

有些研究报道，男性和女性的醛固酮水平也不一致。有一项社区为基础的大样本研究表明女性的血清醛固酮水平高于男性[19]。最近有动物研究也表明，限制钠饮食的雌性小鼠比雄性小鼠显著增加肾上腺 CYP11B2 表达和血浆醛固酮水平[20] [21]。Caroccia 等人发现了其中的机制，肾上腺生理可能受到性激素的调节。在人肾上腺皮质细胞中，雌二醇以受体依赖的方式调节醛固酮的合成，G 蛋白偶联受体-1 (GPER1)和雌激素受体-β (ERβ)的激活分别促进醛固酮的分泌[22]。此外，Shukri MZ 等人发现，在低盐饮食和无盐饮食中，AngII 增加醛固酮产生的作用在女性中比在男性中更明显，但这仅适用于年龄小于 51 岁的女性[23]。这可能解释与同龄男性相比，育龄女性患心血管(CV)事件的风险更低，血压值也更低，尤其是未绝经的女性中[23]。还有，女性体内的醛固酮水平与月经周期的变化有关。有证据表明，在月经周期的黄体期，女性体内的醛固酮水平高于男性，但在排卵期或月经期则不然[24]。然而，这些研究样本量小或没有控制钠摄入量或姿势等影响 RAAS 活性的主要因素，研究结论存在争议，提示往后的研究中进一步探索性别差异，这对男女性的醛固酮街道的高血压及心血管疾病的针对性预防策略中起一定的作用。

4. 肥胖相关指标

既往的诸多研究表明体重指数及肥胖相关指标与醛固酮浓度呈正相关。来自较小人群的非洲白人成人的研究结果支持了包括身体质量指数、腰围和腰高比在内的肥胖人体测量指标与醛固酮的横断面关联[25]。在非西班牙裔白人中，包括 BMI、内脏脂肪组织和腰围在内的肥胖指标与醛固酮呈正相关[26]。BMI 与醛固酮相关的潜在机制是脂肪因子。较高的 BMI 水平与较高的瘦素水平和较低的脂联素水平相关[27]。尽管 BMI 是衡量肥胖最广泛使用的临床工具，脂肪分布是代谢健康的一个更强的预测指标[28]。相关研究显示，不仅脂肪组织本身可以分泌醛固酮[29]，有趣的是，内脏脂肪组织能够分泌醛固酮，还能分泌醛固酮释放因子，刺激肾上腺醛固酮分泌，脂肪细胞衍生因子可能参与肾上腺醛固酮的合成[30]。瘦素是肾上腺肾小球带细胞中 CYP11B2 表达和醛固酮生成的直接调节因子[31]。瘦素能够直接激活肾上腺的 CYP11B2，从而通过 Ca^{2+}依赖机制增加醛固酮的产生，该机制不依赖于 RAAS 和交感神经系统[31]。也研究显示减肥会降低醛固酮水平[32]。

5. 吸烟

以前关于急性和慢性吸烟与醛固酮的关系的数据是混合的。一项研究指出，吸烟后醛固酮水平急剧上升，在 30 分钟后达到峰值[33]。Laustiola 等人指出，与不吸烟的同卵双胞胎相比，长期吸烟者的基线醛固酮水平更高[34]。近日在美国的杰克孙心脏研究中表明，理想吸烟与较低的醛固酮有最大程度的相关性[15]。然而，一些基于人群的研究并没有显示出吸烟者和非吸烟者之间醛固酮水平的显著差异[35]。近日在美国的杰克孙心脏研究中表明，理想吸烟与较低的醛固酮有最大程度的相关性[15]，本研究中还发现了显著的性别差异，与目前吸烟者相比，男性不吸烟者的醛固酮降低了 4%，而女性醛固酮显著降低了

42% [15]。香烟烟雾中含有 4000 多种化学物质；其中一种主要的化学物质是尼古丁。在培养的人内皮细胞中，尼古丁增加了血管紧张素转换酶的表达和活性[36] [37]。血管紧张素转换酶将血管紧张素 I 转化为血管紧张素 II，血管紧张素 II 刺激肾上腺皮质分泌醛固酮。因此，尼古丁通过更高的血管紧张素转换酶活性增加血管紧张素 II，导致吸烟者(尤其是女性)的醛固酮升高，这是由于男性肾上腺对血管紧张素 II 的反应减弱，这可能为吸烟－醛固酮相关性的性别差异提供了一种解释[38] [39]。鉴于香烟中含有大量的化学物质，需要进一步的流行病学和临床前研究来检查吸烟对醛固酮的影响，以澄清这种关系和潜在的性别二态性。

6. 饮酒

既往的几项动物研究中观察到饮酒与醛固酮之间的关系。有个动物实验结果提示酗酒提高血清醛固酮水平[40]。在恒河猴酒精使用模型中，与基线相比，连续饮酒 6 个月和 12 个月后血浆醛固酮显著增加[41]。在多个物种中，循环醛固酮水平与酒精使用呈正相关[42]。其机制可能是酒精中所含的乙醇降低了核受体亚家族 3C 组成员 2 种属(NR3C2)的表达与醛固酮合成相关的基因，并减少 mr 介导的负反馈[41]。这意味着禁酒或控制饮酒对控制醛固酮水平都有影响。

7. 体育活动

先前分析醛固酮和体育活动之间关系的研究没有定论。一项研究表明，有氧运动形式的体力活动会降低醛固酮水平[43]，而另一些研究则表明有氧运动对醛固酮没有影响[44] [45]。有趣的是，可能存在种族/民族差异，一项研究显示，有氧运动训练后，白人的醛固酮水平较低，而非白人没有[44]。然而，既往的一项研究发现，在年轻人或老年人中，长期的耐力训练与醛固酮的减少没有关联[46]。在美国的杰克孙心脏研究中，体育活动与醛固酮无关[15]。有一些证据表明，运动可以降低血浆醛固酮浓度，这是一种对 RAAS 激活的高血压患者特别感兴趣的运动效果[47]。健康受试者较高水平的体力活动(PA)与较低的不良心血管结局风险相关，包括较低的心衰发生率[48] [49] [50] [51]。因此，有规律的体育活动至关重要，而且往后的研究需要进一步证明体育活动与醛固酮水平之间的关系及其中机制。

8. 总胆固醇

总胆固醇是血液中胆固醇的总量，包括高密度脂蛋白(HDL)、低密度脂蛋白(LDL)和甘油三酯的组合，计算公式为 HDL + LDL + (甘油三酯/5)。关于醛固酮与总胆固醇之间关系的数据有限。在大多数非西班牙裔白人中，醛固酮与总胆固醇/HDL 比值[19]，甘油三酯呈正相关，与 HDL 呈负相关[19]。在针对非洲白人成人的小型研究中，胆固醇与醛固酮的相关性发现不一致，包括与甘油三酯呈正相关而不是与总胆固醇呈正相关[52]，总胆固醇和甘油三酯与直立醛固酮呈正相关而与仰卧醛固酮不呈正相关[25]，HDL 与醛固酮呈负相关，但与总胆固醇或甘油三酯无相关报道[26]。从机制的角度来看，胆固醇通过各种脂蛋白成分调节醛固酮的合成和调节。极低密度脂蛋白通过多种信号通路(STaR 和 CYP11B2)诱导醛固酮合成[53]。LDL 为醛固酮的合成提供底物(胆固醇)，从而增加醛固酮水平[25]。醛固酮在人肾上腺皮质细胞中的产生是由 HDL2 通过增加 CYP11B2 的表达来刺激的[54]。与胆固醇调节功能一致，他汀类药物可降低醛固酮水平[55]。

9. 血糖

在美国的杰克孙心脏研究中的非洲白人中，醛固酮与胰岛素抵抗、葡萄糖和 4 年的葡萄糖变化呈正相关，与其他种族/民族的研究一致[56]。相关研究证实了其中机制，醛固酮过量会损害胰岛素分泌和胰岛素敏感性[57]。醛固酮通过抑制胰岛素信号和通过脂肪细胞、骨骼肌和血管平滑肌细胞中 glut-4 易位的

胰岛素刺激的葡萄糖摄取来增加胰岛素抵抗[58]。此外，醛固酮损害脂肪因子和核受体，通过脂肪组织炎症改善胰岛素敏感性，包括脂联素和过氧化物酶体增殖物激活受体[59]。因此，服用降糖药物可降低醛固酮水平。

10. 血钠、血钙及血钾水平

对膳食钠摄入量增加的经典生理适应是抑制盐潴留，激素 AngII 和醛固酮[60]。然而，新出现的临床和实验数据表明，饮食中的盐摄入量以性别特异性的方式控制醛固酮的产生，有利于女性的高产量，这可能是导致女性盐敏感性高血压患病率较高的一个象征性机制[61]。钙流入对于持续的醛固酮分泌反应以及调节蛋白激酶 C(PKC)活性至关重要[62] [63]，与 AngII 类似，细胞外钾水平的小幅增加也通过肾小球细胞膜的去极化和电压依赖性钙通道的激活(短暂的 t 型和持久的 l 型)刺激钙内流而实现。同样与 AngII 一样，这种内流是钾反应所必需的，因为抑制钙的内流消除钾刺激的醛固酮分泌[64] [65]。一个与钙内流相关的有趣的发现是，将钾水平降低到 2 mM 可以抑制血管内皮素诱导的醛固酮产生，可能是通过抑制血管内皮素诱导的钙内流[66]。可以推测，这一机制是在低血清钾水平的条件下，防止血管内皮素刺激的醛固酮分泌，否则会导致钾的过度排泄，从而导致严重的，可能致命的低钾血症。

11. 心理状态

随着社会的快速发展，人们的生活、工作压力越来越大，人们心理健康问题越来越严重，患抑郁和(或)焦虑的人数越来越多，故健康心理方面的问题引起大家的关注。既往有关醛固酮与抑郁、焦虑之间的研究并不少。在一项调查抑郁症 RAAS 的研究中报告了 65 名抑郁症患者血浆醛固酮水平升高的几率是 65 名对照组的 2.77 倍[67]。最近的研究报告唾液醛固酮与抑郁发作的严重程度、持续时间和结局相关[68]。矿物皮质激素受体(MR)和肾素醛固酮－血管紧张素系统在抑郁和焦虑的病理生理学中受到了关注，尽管其背后的病理生理学尚未完全了解[69]。在动物模型中，醛固酮与炎症相关的潜在分子机制是其与脂多糖(即内毒素)协同激活 toll 样受体 4 (TLR4)。这种分子机制可能有助于增加脆弱性，以发展焦虑和抑郁样行为[70] [71] [72]。此外，女性患者中，较高的焦虑水平与显著较高的肾素浓度相关，而较高的抑郁评分与较高的醛固酮水平相关[69]。总之，这些足够表明维持良好的心理状态可能与维持醛固酮水平具有潜在的意义。

12. 小结

醛固酮作为 RAAS 轴中的最后一个成分，在高血压、心脑血管疾病及代谢疾病的发生和发展中起重要作用。随着对 RAAS 系统中各成分的深入研究，越来越多的研究证明醛固酮分泌及调节相关的一些因素，如与年龄，性别，体重指数，吸烟，饮酒，体育活动，总胆固醇，血糖，血钠、血钙、血钾浓度、心理状态等因素相关。其中，体育运动与醛固酮之间的研究，可能因为种族/民族差异，样本量小，未充分考虑混杂因素等原因，目前的研究结论还存在一些争议。针对干预和控制醛固酮直接或间接影响导致的高血压和心脑血管、代谢疾病的发生和进展，早认识醛固酮水平升高的相关因素至关重要。因此，往后的研究需要对体育活动进行客观测量的流行病学和临床试验研究，以提高对体育活动对醛固酮的急性和慢性影响的理解。

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