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Apelin的抗氧化性对氨基糖苷药物所致听力损失保护作用的研究进展

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摘 要

Apelin是指G蛋白偶联受体APJ中的一种特异性内源性配体，其在体内外均可抑制氧化应激和细胞凋亡。氨基糖苷类抗生素所导致的耳毒性即指氨基糖苷类抗生素所致的机体内耳机构(耳蜗和前庭器官)及其功能(听力和平衡觉)的损害。目前部分研究已经证明Apelin对于氧化应激的调节有助于改善氨基糖苷类抗生素所带来的药物耳毒性影响。本文将从Apelin对氧化应激机制的调控和活性氧(ROS)过量堆积是氨基糖苷类抗生素所致的耳毒性的重要原因，以及Apelin可以通过抑制氧化应激从而减轻氨基糖苷抗生素所导致的听力损失进行综述，旨在为氨基糖苷类临床药物所致耳毒性的毒副作用寻找科学可行的临床思路及新型防治策略。

关键词

Apelin，氧化应激，氨基糖苷类抗生素，听力损失，耳毒性

Research Progress on the Protective Effect of Apelin’s Antioxidant Activity on Aminoglycoside Induced Hearing Loss

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Abstract

Apelin refers to a specific endogenous ligand in G protein-coupled receptor APJ that inhibits oxidative stress and apoptosis both *in vivo* and *in vitro*. Ototoxicity caused by aminoglycoside antibiotics refers to the impairment of inner ear organs (cochlea and vestibular organs) and their functions (hearing and balance) caused by aminoglycoside antibiotics. Some studies have shown that Apelin's regulation of oxidative stress helps to ameliorate the ototoxic effects of aminoglycoside antibiotics. This article will review the regulation of oxidative stress mechanism by Apelin and the important cause of ototoxicity caused by aminoglycoside antibiotics due to excessive accumulation of reactive oxygen species (ROS), and how Apelin can reduce hearing loss caused by aminoglycoside antibiotics by inhibiting oxidative stress. The aim is to find scientific and feasible clinical ideas and new prevention strategies for the side effects of ototoxicity caused by aminoglycoside drugs.

Keywords

Apelin, Oxidative Stress, Aminoglycoside Antibiotic, Hearing Loss, Ototoxicity

1. 引言

Apelin 是 G 蛋白偶联受体(APJ)中的一种内源性的配体，其大范围分布于人和动物的多种器官系统之中[1]。近年来，诸多研究证实了 Apelin/APJ 系统在抗炎、抗凋亡、抗氧化应激、调节自噬、阻断兴奋性毒性等神经保护作用，比如 Apelin13 可以抑制小胶质细胞、星胶质细胞等炎症细胞，也可显著抑制缺血脑组织氧化应激的产生，提高超氧化物歧化酶(SOD)的含量，证明了其有可能成为神经系统疾病的一个新颖的治疗靶点研究方向[2]。听力损失常见原因就是由于内耳耳蜗毛细胞、螺旋神经节等不可逆的死亡，这些细胞死亡原因可能与细胞过氧化即活性氧(ROS)过量堆积密切相关。因此，Apelin 的抗氧化应激等机制方面的研究将有助于帮助我们为氨基糖苷类药物所致听力损失带来新的思路。

2. 耳毒性

耳毒性于 2018 年经过听力损失药物干预耳毒性工作组的共同研究决定，将其的定义定为由于暴露于某些某些药物、化学物质及相关电离辐射造成的内耳损害(主要是对耳蜗和前庭器官的损害) [3]。耳毒性通常被认为是一种对于耳部尤其是内耳的一种现象，由于内耳的大多数感觉功能与神经系统密不可分，耳毒性药物也会影响某些相关的中枢神经通路，当然其中也有包含有关听觉的神经通路，因而耳毒性的发生常常与神经损害密不可分[4] [5]。听觉是我们人类敏锐的感知能力之一，丧失良好听觉功能的人群将会不可避免地减少自身与亲朋好友之间的言语互动，并减少对周围环境声音的捕捉，相较于听力水平正常的人群变得不易产生安全感[6]。氨基糖苷类药物在临床上的广泛应用时期较早，同时相关的剂量分层方案和有限的纯音测听测试结果并不总是包括听力测定中高于 8 kHz 的频率，因而氨基糖苷类抗生素治疗后导致的听力下降发病率目前并不完全清楚，虽然如此，有数据统计表明接受氨基糖苷类抗生素治疗数天的患者中发生听力下降的患者约占到 20%~63% [7]-[9]。

2.1. 氨基糖苷类药物进入内耳的方式

血迷路屏障(BLB)将内耳中的耳蜗细胞及液体环境与血液分隔开来，与血脑屏障作用机理相似。内耳耳蜗血管的内皮细胞通常以紧密连接的方式结合在一起，通过这种紧密连接形成初级的血迷路屏障，因此大分子物质和血细胞并不容易通过血迷路屏障[10]，内耳耳蜗内的淋巴液由其他细胞外液所含有的典型离子组成，并且液体的分子量体积较大[11]。尽管全身静脉给药的氨基糖苷类抗生素可以通过血液循环而进入内耳毛细胞基底外侧膜周围的外淋巴间隙，但是通常情况下氨基糖苷类抗生素较少通过此结构进入耳蜗毛细胞[12] [13]并且耳蜗内淋巴较血液或耳蜗外淋巴具有+80 mV 的正电位，这对于听力的敏感性有重要意义。通过紧密连接的血管上皮细胞包围较小体积的内淋巴，以防止内淋巴与外淋巴相混合(由此避免听力损失)，同时内淋巴的高电位和其含有的离子组成是由耳蜗侧壁血管纹的高代谢活性细胞造成[14] [15]。其中对于系统给药的氨基糖苷类抗生素和顺铂药物在耳蜗的主要运输途径均为主要从血管纹处的毛细血管进入耳蜗，其中氨基糖苷类抗生素进入内淋巴的离子通道或转运蛋白尚未完全确定[3]。

2.2. 氨基糖苷类抗生素导致耳毒性的相关机制

对于哺乳动物而言，氨基糖苷类抗生素对于肾脏的近端小管细胞和内耳的耳蜗毛细胞都具有明显的毒副作用，有研究表明，如果可以及时停药，由于肾脏近端小管细胞具有再生能力，氨基糖苷类抗生素对于肾脏近端小管的毒性作用是可以逆转的，但是对于内耳的耳蜗毛细胞而言，由于耳蜗毛细胞几乎没有再生功能，所以药物导致的损伤通常将不可逆转[16]-[18]。在耳蜗毛细胞内，氨基糖苷类抗生素可与多种蛋白质结合，这些结合可以诱导毛细胞死亡的多种机制，比如内质网应激和线粒体完整性的破坏，该过程可以导致过量活性氧的产生使得 ROS 大量堆积进而导致细胞死亡，尤其是毛细胞死亡[19]-[22]。比如庆大霉素对内耳耳蜗毛细胞的毒性作用就与氧化应激过程中产生的大量 ROS 密切相关[23]。目前已有相关研究表明，氧化应激有可能是氨基糖苷类抗生素导致耳毒性的重要原因[24] [25]。耳蜗毛细胞在被氨基糖苷类抗生素损伤后，其内含有的活性氧(ROS)将显著增多。有报道称多种类型的抗氧化剂通过抑制过氧化减少 ROS 的产生对于保护耳蜗毛细胞有重要作用，说明抑制氧化应激可以使得耳蜗毛细胞对于氨基糖苷类抗生素的耳毒性有一定抗性[26]。同时有研究表明被新霉素处理的内耳耳蜗毛细胞中，自噬活性会显著增强，被经典自噬抑制剂 3-MA 处理过后会导致毛细胞中 ROS 高积累，表明自噬对于降低氨基糖苷类抗生素所导致耳毒性的作用机理上发挥着重要的抗氧化作用[27]。

3. Apelin

Apelin 是由基因 APLN 编码产生，APLN 基因位于 X 染色体 Xq25-26 位，可编码氨基酸前肽高达 77 种[28]，它有一个强疏水性的 N 末端区域结构，有可能是与受体相互影响的作用序列，还有一个 C 末端，与其生物活性相关[29]，成熟的 Apelin 不具有桥结构而是以单体的形式存在[30]，是 G 蛋白偶联受体 APJ 的内源性配体。后来有研究表明 Apelin 是一种可以由牛胃中提取的神经肽，根据最终产物氨基酸长度被划分为 Apelin-36、Apelin-17、Apelin-13 不同的亚型，与其余的 Apelin 亚型相比，Apelin-13 表现出的活性最高[29]。研究表明，Apelin-13 对神经退行性疾病中的氧化应激状态具有一定程度的神经保护作用[31]。

3.1. Apelin 的抗氧化性

有相关研究表明，经过 Apelin 治疗的糖尿病大鼠的耳蜗总抗氧化状态(TAS)较未经处理的糖尿病大鼠显著升高，同时其总氧化状态(TOS)和氧化应激指数(OSI)明显下降[32]。研究表明，Apelin 可以增强线粒体膜电位，以此提高过氧化能力清除过量的 ROS，最终减少细胞凋亡保护脊髓受损后损伤的神经元[33]。也有研究表明，Apelin 可以增强水牛卵巢卵泡颗粒细胞的抗氧化能力[34]。综合来看，Apelin 抗氧

化清除 ROS 的功能已得到广泛认可，但到目前为止，Apelin 在听力保护方面发挥抗氧化作用的研究相对较少，这意味着 Apelin 在听力保护的应用方面或许存在巨大潜力。

3.2. Apelin 抗氧化的意义及作用机制

由于 Apelin 其所具有一定程度上的抗氧化能力，因此其在某些涉及到细胞层面损伤的疾病上具有一定的保护及治疗作用[35] [36]比如，Apelin 可以通过促进线粒体超氧化物歧化酶以及过氧化氢酶和谷胱甘肽过氧化物酶的活性，来抑制羟基自由基以及丙二醛的生成，进而减少肾缺血再灌注后所导致的损伤[37]。同样的，Apelin 也可以通过减少心肌梗死后血清中 LDH、CK-MB 和 MDA 水平，减少心肌梗死大鼠模型中氧化应激所带来的心肌损伤，这个过程中同样抑制了损伤组织的脂质过氧化，以此来达到保护心脏的作用[38]。而且，近期有研究表明，伴随着 Sirt1 的上调和 NF-κB/p53 的下调，Apelin-13 可以抑制环磷酰胺诱导的氧化应激[39]。过量的 ROS 的产生及线粒体功能的障碍是耳蜗细胞凋亡的因素，也是顺铂导致药物性耳聋的关键因素[40]，而 Apelin 对于抑制氧化应激，清除过量 ROS 的作用，或许可以成为我们防治氨基糖苷类药物所致耳毒性的关键靶点。

4. 讨论与展望

目前，通过查阅相关资料我们不难发现，药物性听力损失仍然是国内乃至国际普遍关注的热点问题，这其中尤其是氨基糖苷类抗生素所致的药物性耳聋更由于氨基糖苷类抗生素应用的广泛性而备受关注，虽然目前临床上对于氨基糖苷类药物的使用已远远不及较早时期的使用规模，但对于已经由于药物造成听力损失或正在经历听力下降的患者我们仍然应予以重视。目前对于 Apelin 用以改善氨基糖苷类抗生素所致药物性耳聋的研究还少之又少，相关机制也尚不明确，但是 Apelin 在其它系统如：代谢、神经、循环疾病的发生发展上，已被证实通过其抗氧化的作用确实起到了一定的改善效果。而且通过以上趋势及 apelin 用于治疗其他疾病的研究来看，我们有理由相信 Apelin 用于治疗氨基糖苷类抗生素所致药物性耳聋上有较高的临床价值。如前所述，值得我们关注的是，虽然氨基糖苷类抗生素所致耳毒性的相关机制已有较为广泛的研究，但在 Apelin 和其对治疗药物耳毒性所致听力下降相关联方面的研究仍有不足，尤其在对于氨基糖苷类药物所致听力下降的研究中相对空白，因而以 Apelin 作为临床药物用于氨基糖苷类抗生素所致药物性耳毒性的防治是极具前瞻性的，研究 Apelin 在听力保护领域方面的作用将可能为日后临床上药物性耳聋的患者的治疗带来新的思路。

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