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烟酰胺单核苷酸在代谢性疾病治疗中的研究进展

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摘 要

烟酰胺单核苷酸(NMN)作为烟酰胺腺嘌呤二核苷酸(NAD^+)的前体分子，近年来在代谢性疾病治疗和衰老干预方面引起了广泛关注。NAD^+在细胞内发挥着多种重要的生物学功能，包括能量代谢、DNA修复、免疫调节及抗衰老等。随着年龄增长，NAD^+水平逐渐下降，这与多种代谢性疾病如糖尿病、肥胖症、非酒精性脂肪性肝病及衰老过程密切相关。NMN通过提升NAD^+水平，已经在动物实验和初步临床研究中表现出显著的治疗潜力，尤其在改善代谢紊乱、减缓衰老及相关并发症方面展现了积极的效果。研究表明，NMN能够调节多个关键的代谢途径，如胰岛素信号通路、线粒体功能及抗氧化反应等，从而改善代谢性疾病的病理变化。本文综述了NMN在代谢性疾病中的作用及机制，探讨了其临床应用前景，并提出了当前研究中的不足与挑战。未来的研究应聚焦于临床验证、NMN的生物利用度、作用机制的深入探索，以及与其他治疗策略的协同效应，为NMN的临床应用提供更加坚实的科学依据。

关键词

烟酰胺单核苷酸，代谢性疾病，NAD^+前体，衰老

Advances in the Study of Nicotinamide Mononucleotides in the Treatment of Metabolic Diseases

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Abstract

Nicotinamide mononucleotide (NMN), as a precursor molecule of nicotinamide adenine dinucleotide

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(NAD+), has attracted much attention in recent years in the treatment of metabolic diseases and aging interventions. NAD+ performs a variety of important biological functions in cells, including energy metabolism, DNA repair, immune regulation, and anti-aging. NAD+ levels decline with age, which is closely related to a variety of metabolic diseases such as diabetes, obesity, non-alcoholic fatty liver disease, and the aging process. NMN has demonstrated significant therapeutic potential in animal experiments and preliminary clinical studies by elevating NAD+ levels, and has shown positive effects in improving metabolic disorders, slowing down the aging process, and related complications. Studies have shown that NMN can modulate several key metabolic pathways, such as insulin signaling pathway, mitochondrial function and antioxidant response, and thus ameliorate pathological changes in metabolic diseases. This article summarizes the role and mechanism of NMN in metabolic diseases, discusses the prospect of its clinical application, and presents the shortcomings and challenges in current research. Future studies should focus on clinical validation, bioavailability of NMN, in-depth exploration of the mechanism of action, and synergistic effects with other therapeutic strategies to provide a more solid scientific basis for the clinical application of NMN.

Keywords

Nicotinamide Mononucleotide, Metabolic Disease, NAD+ Precursor, Aging

1. 引言

烟酰胺腺嘌呤二核苷酸(NAD+)的前体分子近年来引起了广泛关注[1]。NAD+在细胞内发挥着多种关键生物学功能，包括参与能量代谢、DNA 修复、细胞衰老和免疫调节等过程[2] [3]。随着年龄的增长和代谢性疾病的蔓延，NAD+水平通常呈现下降趋势，这直接导致了细胞功能的退化和多种代谢性疾病的发生，如 2 型糖尿病、心血管疾病、脂肪肝和肥胖症等。作为 NAD+的有效前体，NMN 通过提升 NAD+水平[4] [5]，已在多项动物实验和初步的临床研究中显示出显著的治疗潜力，尤其在改善代谢紊乱、延缓衰老和减缓相关并发症的进程中展现了积极的效果[5]。随着全球肥胖和糖尿病患病率的上升，代谢性疾病已成为严重的公共卫生挑战。寻找能够改善这些疾病的新策略成为了生物医学领域的重要研究课题。NMN 的潜力不仅在于其可以恢复 NAD+水平，还因其能够调节关键的代谢途径，如胰岛素信号通路、线粒体功能和氧化还原状态等[6] [7]，进而对代谢性疾病的治疗产生深远影响。尽管 NMN 在动物模型中的疗效得到了一定的验证，如何在人体中进一步验证其安全性和有效性，尤其是在不同代谢疾病中的应用，仍然是当前研究的重点。

本篇文献综述的主要目的是系统地总结近年来关于 NMN 对代谢性疾病作用的研究进展，分析其潜在的机制，并探讨 NMN 在临床治疗中的前景。通过综合各类实验数据，为 NMN 作为一种有前景的代谢性疾病治疗手段提供科学依据，并为未来的研究提供指导。

近年来，随着全球老龄化的加剧，寻找延缓衰老和改善代谢性疾病的有效手段成为了生物医学研究的重要课题。烟酰胺单核苷酸(Nicotinamide Mononucleotide, NMN)，作为一种 NAD+前体分子，因其在延缓衰老、改善代谢紊乱和抗衰老的潜力，得到了广泛关注。NAD+ (烟酰胺腺嘌呤二核苷酸)是细胞中多种重要生物化学反应的辅酶，包括 DNA 修复、细胞代谢、免疫调节和衰老等过程[8] [9]。随着年龄的增长，体内 NAD+水平逐渐下降，导致细胞功能受损，进而引发一系列与衰老相关的疾病。为了恢复 NAD+水平并延缓衰老进程，NMN 的补充在多种疾病模型中展现了显著的疗效。

2. NMN 对糖尿病肾病的影响

在糖尿病及其相关并发症中，NAD^+水平的下降是其代谢失调的一个重要机制。多项研究表明，NMN 能够通过提升 NAD^+水平改善糖尿病相关的代谢障碍。研究发现，在 db/db 糖尿病小鼠中，NMN 的短期治疗显著改善了尿白蛋白排泄、肾脏组织的病理改变和 Sirt1 表达水平，从而减缓了糖尿病肾病的进展[10]-[13]。NMN 通过激活 Sirt1 和 NAD^+再循环途径对糖尿病肾病起到了远期的保护作用，这一发现为 NMN 在糖尿病肾病治疗中的潜力提供了新的证据[14]-[16]。此外，相关的机制研究还发现 NMN 能够促进糖尿病小鼠中 Sirt1 和 Nmnat1 的表达，维持肾脏的 NAD^+浓度，从而改善糖尿病引起的肾脏损伤[17]-[20]。

3. NMN 对心脏代谢及功能的改善作用

心脏代谢紊乱，尤其是脂肪过量引起的心肌病，是代谢性疾病中常见的并发症[21] [22]。高脂饮食会导致脂肪在心脏中积累，从而引发心脏功能障碍和炎症反应[23]。研究发现，NMN 通过维持细胞内的 NAD^+水平，能够恢复心肌细胞中的质子泵(v-ATPase)活性，从而改善脂质代谢，减少脂肪积累，减轻心脏功能受损[24]-[26]。研究指出，NMN 能够通过促进 v-ATPase 的重组，防止 CD36 受体介导的脂肪积累和 TLR4 受体的炎症反应，从而改善心脏功能和胰岛素抵抗[27]-[29]。这一发现为 NMN 在脂肪引起的心脏病防治中提供了理论支持。

4. NMN 在肝脏代谢及非酒精性脂肪性肝病中的作用

非酒精性脂肪性肝病(NAFLD)是一种由脂肪积累引起的肝脏疾病，与肥胖和胰岛素抵抗密切相关[30]。最近的研究表明，NMN 不仅能够改善肝脏代谢紊乱，还能减轻肝脏的氧化应激和脂肪积累[31]。研究者通过转录组和代谢组分析，发现 NMN 能够有效调节 NAFLD 小鼠的脂质代谢，增加不饱和脂肪酸和多不饱和脂肪酸的合成，抑制饱和脂肪酸的积累[32] [33]。NMN 通过激活细胞色素 P450 (CYP450)酶的代谢作用，促进花生四烯酸和亚油酸的代谢，进而减轻肝脏脂肪变性和氧化应激[34]。这一研究揭示了 NMN 在 NAFLD 治疗中的潜力，为其未来的临床应用提供了基础。

5. NMN 在代谢综合征中的作用

随着年龄的增长，人体的代谢功能逐渐衰退，导致代谢综合征的发生。尤其是在肥胖和 2 型糖尿病患者中，NAD^+的水平显著下降，进一步加重了胰岛素抵抗和代谢紊乱[35]。一项临床试验表明，NMN 的补充能够改善围绝经期女性的胰岛素敏感性和肌肉重塑[36]。通过激活肌肉中的胰岛素信号传导和促进 AKT 及 mTOR 的磷酸化，NMN 能够有效改善肌肉的代谢功能，减轻与衰老相关的代谢紊乱[37] [38]。这一发现强调了 NMN 在抗衰老及代谢性疾病治疗中的重要作用。

6. NMN 对代谢相关认知功能障碍的作用

除了在代谢疾病中的作用，NMN 还被证明能够改善糖尿病引起的认知功能障碍[39]。许多研究表明，糖尿病患者经常伴随认知功能下降，主要原因是脑部 NAD^+水平的减少[40]。NMN 作为 NAD^+的前体物质，可在细胞内转化为 NAD^+。NAD^+是细胞能量代谢和信号转导中的关键分子，其水平的提升对线粒体功能至关重要。补充 NMN 能够增加线粒体中的 NAD^+含量，为线粒体的能量代谢和各种生物化学反应提供充足的底物。研究发现 NMN 还能够通过增加大脑中的 NAD^+浓度，激活 SIRT1 途径，SIRT1 可以去乙酰化并激活 PGC-1α，PGC-1α 是调节线粒体生物发生和功能的关键转录因子，能够促进线粒体相关基因的表达，增加线粒体数量和改善线粒体功能，从而改善糖尿病大鼠的记忆力和学习能力[41]。NMN 的治疗不仅恢复了糖尿病大鼠海马区的 NAD^+水平，还防止了 CA1 神经元的丧失，并改善了蛋白质去乙酰化作用，进而保

护了神经功能[42] [43]。这一研究为 NMN 在糖尿病相关认知功能衰退的治疗提供了重要线索。

7. NMN 的给药途径和使用剂量

NMN 的给药途径主要包括口服、舌下含服及静脉注射[39] [44]。口服是最常见且方便的给药方式。大量研究表明其安全有效，如在一项 12 周的随机、双盲、安慰剂对照试验中，42 名健康老年男性每天口服 250 mg NMN，血液中 NAD^+浓度显著升高且耐受性良好。口服 NMN 后，其通过小肠吸收迅速进入血液，转化为 NAD^+发挥作用[44]。舌下含服可使 NMN 经口腔黏膜直接进入血液循环，避免肝脏首过效应，提高生物利用度，但每次含服量有限[39]。静脉注射能快速将 NMN 输送到体内各组织，适用于需要快速提升体内 NAD^+水平的研究或治疗，但在临床研究和实际应用中相对较少[40] [44]。

8. NMN 的临床应用前景和挑战

尽管 NMN 在多种动物模型中显示出良好的治疗效果，但其在人类中的疗效和安全性仍然需要进一步验证[45]-[47]。临床试验已初步证明，NMN 补充能够有效提高血液中的 NAD^+浓度，并在一定程度上改善衰老引起的肌肉功能下降和运动能力[48] [49]。然而，NMN 对体成分、代谢综合征和其他衰老相关疾病的长效疗效仍需通过更大规模、更长时间的临床研究来进一步验证。

9. 小结与展望

综合来看，NMN 作为 NAD^+的前体分子，在多种代谢性疾病和衰老相关疾病中展现了显著的治疗潜力。研究表明，NMN 通过恢复 NAD^+水平，改善线粒体功能、胰岛素信号通路、抗氧化反应等关键生物过程，能够缓解糖尿病、心血管疾病、肝病等代谢性疾病的病理变化。此外，NMN 还显示出在延缓衰老和改善认知功能方面的潜力。尽管 NMN 作为一种 NAD^+前体分子在多个代谢性疾病中的研究取得了初步成果，但当前的研究仍存在一些不足和挑战。首先，大多数研究仍集中在动物实验中，尽管有一些小规模的人体临床试验，但关于 NMN 在不同人群(如老年人、肥胖患者、糖尿病患者等)中的长期疗效和安全性尚缺乏充分的证据。其次，NMN 的生物利用度及其在体内的代谢过程仍未被完全阐明，如何确保其能够有效地进入靶细胞并提高 NAD^+水平，仍是一个亟待解决的问题。第三，尽管已有研究揭示了 NMN 在改善代谢性疾病中的潜在机制，但这些机制的全面性和复杂性仍需进一步探讨，特别是在不同疾病状态下 NMN 的具体作用路径和分子靶点尚不清楚。

未来的研究应着重解决这些不足。首先，开展更多的多中心、大样本、长期的临床试验，评估 NMN 对代谢性疾病的长期效果及安全性，以便为其临床应用提供坚实的证据支持。其次，进一步探索 NMN 的生物利用度和代谢机制，以便改进其给药方式和剂量，优化其治疗效果。此外，研究人员还应深入探讨 NMN 在不同代谢性疾病中的作用机制，特别是其在糖代谢、脂代谢和线粒体功能中的调控作用，揭示其在细胞层面和分子层面上的作用靶点，以便为精准医学提供新的思路。最后，结合基因组学、代谢组学等前沿技术，开展更为细致的研究，探索 NMN 与其他干预手段(如饮食、运动等)的协同效应，寻找最有效的治疗策略。

NMN 作为一种潜力巨大的代谢性疾病治疗分子，展示了其在改善代谢紊乱和延缓衰老方面的广泛应用前景。然而，要实现 NMN 在临床治疗中的广泛应用，仍需解决多方面的问题，未来的研究应进一步深化对 NMN 作用机制的理解，提升其治疗效果，并确保其长期安全性。

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