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亚精胺改善代谢性疾病的研究进展

王泷彬[1,2],艾锐泽[3],张翊娟[1,2],黄启超[4],樊晓霞[1*],季乐乐[2*]

(1 延安大学医学院基础医学院,延安 716000;2 空军军医大学基础医学院基础医学国家级实验教学示范中心,西安 710032;3 空军军医大学基础医学院学员二大队,西安 710032;4 空军军医大学基础医学院生理与病理生理学教研室,西安 710032)

摘 要:亚精胺(spermidine)是一种广泛存在于生物体内的多胺类化合物,在衰老研究领域备受关注。它通过诱导细胞自噬、促进eIF5A的hypusine修饰以及抑制炎症反应与细胞凋亡等多种途径,发挥延缓细胞衰老、维持机体稳态等作用。随着亚精胺在代谢调控中的作用被逐步揭示,其在代谢性疾病防治中的潜力也愈发凸显。多项研究显示,膳食补充亚精胺能够有效延缓糖尿病和心血管疾病等多种代谢性疾病的发生与发展。本综述系统总结亚精胺在代谢性疾病中的作用机制与研究前沿,进而探讨其作为营养干预靶点的应用前景与临床干预潜力,以期为相关疾病的防治提供新思路。

关键词:亚精胺;线粒体自噬;hypusine修饰;胰岛素抵抗;代谢性疾病
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Research progress on spermidine for the amelioration of metabolic diseases

WANG Shuang-Bin[1, 2], AI Rui-Ze[3], ZHANG Yi-Juan[1, 2], HUANG Qi-Chao[4], FAN Xiao-Xia[1*], JI Le-Le[2*]

(1 School of Basic Medical Sciences, Medical College of Yan'an University, Yan'an 716000, China; 2 National Demonstration Center for Experimental Basic Medical Science Education, Fourth Military Medical University, Xi'an 710032, China; 3 Second Battalion of Basic Medical College Students, Fourth Military Medical University, Xi'an 710032, China; 4 Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Fourth Military Medical University, Xi'an 710032, China)

Abstract: Metabolic disorders comprise a group of diseases characterized by disturbances in energy metabolism, including major public health challenges such as obesity, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease (MASLD). Spermidine, a ubiquitous, naturally occurring polyamine, is essential for maintaining physiological health and sustaining metabolic balance. In the context of ageing research, spermidine has been shown to exert diverse and significant biological effects. Recent findings have increased interest in its capacity to improve metabolic health. Epidemiological evidence indicates a strong inverse association between dietary spermidine intake and the incidence of diabetes and cardiovascular diseases. Notably, spermidine concentrations decline progressively with age, particularly in elderly populations with a high prevalence of metabolic disorders. However, the mechanisms by which spermidine influences metabolic disease, as well as its therapeutic potential, remain incompletely understood. This review aims to systematically examine the biological roles of spermidine in metabolic disorders and elucidate the molecular mechanisms involved, providing a foundation for novel preventive and therapeutic strategies. This review first outlines the biosynthetic and transport pathways of spermidine, establishing a framework for understanding the origins and regulation of its biological functions. *In vivo*, the mammalian spermidine pool is derived from three primary sources: dietary intake, *de novo* biosynthesis, and gut microbiota-derived production. Its distribution and regulation rely on coordinated enzymatic cascades and membrane transport systems. The review then summarizes and discusses the key molecular mechanisms underlying spermidine's putative protective actions, which include: stimulation of autophagy to remove misfolded proteins and damaged organelles; serving as a substrate

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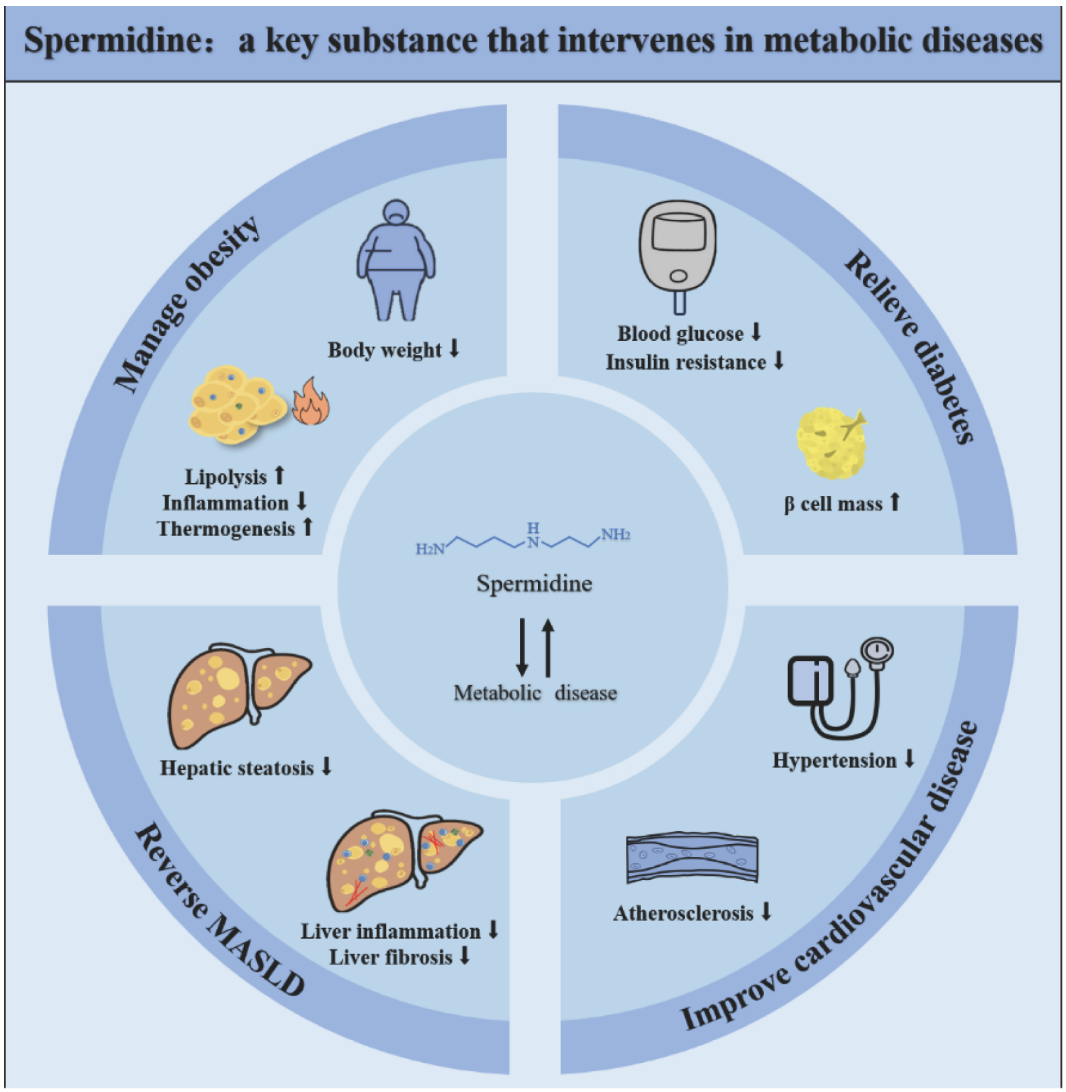
***通信作者**:E-mail:jilele@fmmu.edu.cn(季乐乐);fanxiaoxia01@163.com(樊晓霞)

for eIF5A hypusination, thereby modulating translation and cell proliferation; suppression of pro-inflammatory signaling pathways such as NF-κB to reduce tissue inflammation; inhibition of apoptotic process and reinforcement of antioxidant defense to promote cell survival; and optimization of mitochondrial function to enhance metabolic efficiency. These interconnected processes establish spermidine as a critical regulator of metabolic stability. Through these mechanisms, spermidine demonstrates broad prophylactic and therapeutic potential across a spectrum of metabolic disorders. In obesity, it promotes weight management by activating adipose tissue lipolysis, enhancing thermogenesis in brown adipose tissue, and improving gut microbiota composition and intestinal barrier function. In diabetes, it contributes to glycaemic control by improving peripheral insulin sensitivity, preserving pancreatic β-cell function, and alleviating vascular endothelial inflammatory injury. In MASLD, it mitigates hepatic steatosis and inflammation by enhancing fatty acid oxidation, reducing lipid accumulation, and directly improving mitochondrial function, thereby retarding the progression of fibrosis. In cardiovascular diseases, it confers protection against hypertension and atherosclerosis through multiple pathways, including inducing cardiomyocyte autophagy to improve cardiac function and elasticity, modulating blood lipid profiles, inhibiting platelet aggregation, and stabilizing atherosclerotic plaques. In conclusion, spermidine supports metabolic homeostasis through a multifaceted, synergistic network of molecular actions, offering promising avenues for intervention in multiple metabolic disorders, as evidenced by preclinical research. However, its effects are influenced by cellular context and environmental factors, and translation to clinical practice is challenged by limited human trial data, uncertain dose-response parameters, and potential context-dependent adverse effects. Future advancements will require robust clinical studies informed by a comprehensive understanding of its complex molecular interactions and systems-level biology, with the ultimate goal of defining optimal therapeutic parameters and advancing spermidine as a viable strategy for metabolic disease prevention and treatment.



Key words: spermidine; mitophagy; hypusine modification; insulin resistance; metabolic diseases

代谢性疾病是一类以能量代谢失衡为核心病理特征的疾病，涵盖肥胖、2型糖尿病(T2D)以及代谢功能障碍相关脂肪性肝病(MASLD)等重大公共卫生问题[1,2]。作为一种广泛存在于生物体内的天然多胺类化合物，亚精胺在维持宿主健康与代谢稳态等生命活动中发挥核心作用。在代谢性疾病高发的老年人群中，亚精胺水平随年龄增长而逐渐下降[3,4]。在衰老研究领域，亚精胺已被证实具有多重关键生理效应，不限于诱导自噬这一核心机制，更涵盖抗炎、抗氧化、增强线粒体代谢与呼吸，以及改善蛋白质稳态和伴侣蛋白活性等多个层面[5-8]。随着研究深入，其改善代谢健康的潜力也逐渐受到关注。流行病学研究提示，亚精胺的摄入量与糖尿病、心血管疾病发病率显著负相关[9,10]。动物研究发现，富含果糖的西方饮食会诱导小鼠发生代谢功能障碍相关脂肪性肝炎(MASH)，并伴随肝脏亚精胺合酶基因表达下调[11]。口服亚精胺(20 mg/kg)14周可显著降低高脂饮食(high-fat diet，HFD)小鼠的体重、血清甘油三酯、总胆固醇水平并改善胰岛素抵抗[12]。本文就亚精胺在代谢性疾病中的主要作用及其机制予以综述，旨在为代谢性疾病的预防和治疗策略制定提供理论依据。

1 亚精胺的合成及运输途径

在机体内，亚精胺这一核心分子主要通过三种途径维持其稳态：膳食摄入、内源性合成以及肠道菌群[13]。亚精胺广泛存在于大豆制品、发酵食品、坚果、全谷物、肉类以及蔬菜等食物中，其摄入可迅速提升外周血中亚精胺水平，但在吸收过程中易受肠道代谢环境影响[14,15]。亚精胺亦可通过内源性合成途径产生。该合成路径始于精氨酸，其在精氨酸酶(ARG)催化下生成鸟氨酸；鸟氨酸经鸟氨酸脱羧酶1(ODC1)作用转化为腐胺；最终，腐胺与脱羧的S-腺苷甲硫氨酸(dcSAM)在亚精胺合酶(SRM)催化下生成亚精胺。此合成途径具有组织特异性，在肝脏、大脑等代谢活跃的组织中尤为显著[16,17]。部分肠道微生物同样是亚精胺的重要来源。它们合成的亚精胺不仅有助于维持肠道局部的多胺平衡，还能通过肠-肝轴和肠-脑轴等途径系统性调节全身的多胺稳态。长期摄入益生菌双歧杆菌LKM512能有效提高肠道内的亚精胺水平[18-21]。亚精胺的细胞外排主要依赖于经典的酶促反应途径。研究表明亚精胺可通过亚精胺/精胺N1-乙酰转移酶1(SAT1)生成乙酰化亚精胺，直接排出细胞外，该机制在肝脏和肾脏等排泄功能活跃的组织中尤为重要[22,23]。另外，亚精胺的运输也涉及复杂的膜转运机制。溶质载体(SLC)超家族被证实对维持细胞内多胺稳态具有重要作用。在黑色素细胞中，SLC3A2、SLC7A1、SLC18B1及SLC22A18等转运蛋白显著高表达，提示SLC家族介导的转运机制可能在多胺运输中发挥重要调控作用[24]。其中，SLC18B1作为囊泡多胺转运蛋白，在大脑中特异性介导亚精胺的囊泡外排，揭示其在神经系统中所特有的多胺转运方式[25,26]。

2 亚精胺的作用机制

2.1 促进自噬

亚精胺已被证实可在多种衰老研究模型中激活自噬过程，涵盖酵母、果蝇、线虫及哺乳动物细胞等不同物种[27]。在衰老酵母中，亚精胺处理能显著上调包括自噬相关基因7(ATG7)在内的多种巨自噬相关基因。同样，在人类HeLa和HCT116细胞中，亚精胺也通过促进微管相关蛋白1A/1B轻链3-II(LC3-II)的积累和自噬体形成，证实其诱导自噬的能力。其核心机制在于：亚精胺诱导组蛋白H3低乙酰化，通过表观遗传促进自噬相关转录[28,29]。在老年果蝇模型中，5 nmol/L亚精胺的膳食补充能够通过防止大脑中泛素化蛋白质的异常积累，有效维持老年果蝇的自噬相关基因ATG8a蛋白水平，从而抵消年龄增长对其造成的下降影响[30]。在人骨肉瘤U2OS细胞中，亚精胺(100 μmol/L)通过抑制E1A结合蛋白p300的乙酰转移酶活性并间接抑制α-微管蛋白乙酰转移酶1表达，降低包括ATG5、ATG7、ATG12和LC3在内的几种核心自噬蛋白的乙酰化水平并促进微管蛋白去乙酰化，最终保障自噬囊泡的高效运输[31-34]。在肝纤维化的小鼠模型中补充亚精胺(3 mmol/L)5周，可增加微管相关蛋白1S(MAP1S)水平，并与LC3相互作用上调细胞中的自噬通量[35,36]。在自噬功能受损的胶原蛋白VI型α1链基因敲除(*col6a1*$^{-/-}$)小鼠中，补充亚精胺(50 mg/kg)10天，能通过诱导转录因子FOXO3向细胞核的易位，增加包括自噬相关基因LC3和BCL2相互作用蛋白 3

(Bnip3)在内的靶基因的转录[37,38]。

2.2 促进eIF5A的hypusine修饰

亚精胺是真核翻译起始因子5A(eIF5A)发生羟腐胺赖氨酸(hypusine)修饰，从而获得活性所必需的唯一底物[39]。该修饰通路在细胞增殖中发挥核心作用。在衰老小鼠的静止骨骼肌卫星细胞中，亚精胺能通过促进eIF5A的hypusine修饰促进细胞的活化与增殖[40]。在胰岛β细胞中，补充亚精胺可通过诱导eIF5A的hypusine修饰，上调细胞周期素D2的mRNA翻译，最终促进β细胞增殖[41]。在肿瘤方面，hypusine修饰同样具有重要调控功能。补充低剂量亚精胺可通过上调eIF5A的hypusine修饰，促进核因子E2相关因子2(NRF2)的翻译，进而上调血红素加氧酶-1的表达。这一过程增强体外脂质过氧化并提高细胞内Fe^{2+}浓度，最终促进前列腺癌细胞发生铁死亡，发挥抗肿瘤效应[42]。与之相反，在胰腺导管腺癌中，亚精胺依赖的eIF5A的hypusine修饰通过特异性上调关键下游效应因子伪足富非典型激酶1的表达，促进肿瘤细胞增殖并增强化疗耐药[43]。综上所述，亚精胺作为eIF5A实现hypusine修饰的关键因子，不仅调控正常的细胞增殖，同时在肿瘤进程中表现出双向调控特性——既可诱导前列腺癌铁死亡，亦能驱动胰腺癌的进展与耐药。Hypusine修饰在肿瘤中的双向调控特性提示，亚精胺在代谢疾病调控中的作用可能同样复杂，并高度依赖细胞所处的微环境。

2.3 抑制炎症

临床研究发现，新生儿血浆中的亚精胺水平与炎症标志物C反应蛋白呈负相关。为探究其机制，研究人员利用内毒素血症小鼠模型发现，腹腔注射亚精胺能通过eIF5A的hypusine修饰通路，重塑多形核髓系来源的抑制细胞(polymorphonuclear myeloid derived suppressor cells，PMN-MDSCs)的功能，从而有效抑制新生儿炎症[44]。口服亚精胺可缓解HFD饮食诱导的肥胖小鼠脂肪组织炎症。其机制包括：一方面，通过降低关键趋化因子单核细胞趋化蛋白-1的水平，减少巨噬细胞向脂肪组织的浸润；另一方面，通过下调肿瘤坏死因子-α(*TNF-α*)等基因的转录，抑制核心炎症通路的活化[45]。在体外诱导炎症的软骨细胞模型中，亚精胺(0.5 μmol/L)与芳香烃受体相互作用抑制炎症信号核因子κB(NF-κB)的传导，减轻软骨细胞炎症[46]。同样，在实验性自身免疫性脑脊髓炎模型中，亚精胺可通过激活NRF2信号通路来下调NF-κB的活性，进而抑制巨噬细胞中促炎细胞因子和共刺激分子的表达[47]。

2.4 减轻凋亡

在视神经损伤(optic nerve injury，ONI)小鼠模型中，亚精胺抑制ONI诱导的视网膜神经节细胞中的凋亡相关丝裂原活化蛋白激酶途径的激活[48]。在博来霉素诱导肺纤维化模型中，补充亚精胺(50 mg/kg)能降低内质网应激相关蛋白(包括CHOP、GRP78、ATF6和IRE-1)表达，进而减少内质网应激所导致的细胞凋亡[49]。亚精胺联合3-硝基丙酸(3-NPA)处理卵泡颗粒细胞，可显著降低3-NPA诱导的活性氧和丙二醛水平、增强超氧化物歧化酶(SOD)活性，进而降低半胱天冬蛋白酶-3表达并上调BCL-2蛋白水平，最终有效抑制细胞凋亡与坏死[50]。亚精胺也通过激活NRF2/血红素加氧酶-1(HO-1)/谷胱甘肽过氧化物酶4(GPX4)通路改善卵巢储备功能，减少卵泡颗粒凋亡[51]。在D-半乳糖诱导的氧化还原损伤大鼠模型中，持续6周口服亚精胺可增加SOD活性，提高抗氧化能力，抑制细胞凋亡[52-54]。因此，亚精胺不仅通过直接抑制凋亡信号通路发挥作用，还能通过激活抗氧化通路以及减轻内质网应激等多种间接机制抑制凋亡，促进细胞存活。

2.5 改善线粒体功能

研究表明，老年小鼠卵巢中的亚精胺水平降低，补充亚精胺恢复老龄小鼠卵母细胞中烟酰胺腺嘌呤二核苷酸NAD^+水平，改善线粒体功能[55]。补充亚精胺能提高D-半乳糖诱导和自然衰老大鼠脑内线粒体中电子传递链复合物的活性，并增强线粒体抗氧化能力[56]。在老龄果蝇中，亚精胺通过诱导eIF5A的hypusine修饰，促进线粒体蛋白的翻译，从而提升线粒体的基础呼吸、最大呼吸及ATP生成能力[57]。此外，亚精胺还通过激活线粒体自噬以清除功能异常的线粒体，改善认知功能[58]。在肝损伤小鼠模型中，亚精胺治疗能够显著缓解线粒体氧化应激，并清除受损线粒体[59]。亚精胺还可通过上调肝脏中线粒体肉碱棕榈酰基转移酶1α和酰基辅酶A氧化酶的表达，显著增强线粒体的脂肪酸氧化能力[60]。

3 亚精胺改善代谢性疾病

亚精胺在调控自噬、抑制炎症等方面的核心功能，为其在机体代谢稳态中的作用提供理论依据。

近年越来越多证据提示,亚精胺能够有效减轻机体脂肪堆积并改善外周胰岛素敏感性,展现出对肥胖、糖尿病以及相关代谢性疾病的防治潜力,为代谢性疾病干预提供新思路。亚精胺在调节机体代谢方面表现出多重益处:通过促进脂肪分解与产热有效减轻体重,也可通过降低血糖、改善胰岛素抵抗与保护胰岛β细胞等途径缓解糖尿病。在肝脏中,亚精胺能够减轻肝脏脂肪堆积、抑制炎症并延缓纤维化进程。此外,亚精胺还可降低高血压、减轻动脉粥样硬化,发挥心血管保护作用。

3.1 亚精胺与肥胖

在HFD诱导的肥胖小鼠模型中,口服亚精胺展现出显著的体重管理效应及代谢改善作用[61]。在高脂饮食诱导的肥胖小鼠模型中,饮水补充亚精胺可上调棕色脂肪中成纤维细胞生长因子21(FGF21)信号以促进产热,在白色脂肪中提升脂肪甘油三酯脂肪酶(ATGL)与激素敏感性脂肪酶(HSL)表达以增强脂解[62,63]。此外,口服补充亚精胺可以部分恢复微生物种类的存活,降低甘油三酯水平,从而改善与高脂高糖饮食有关的肥胖[64,65]。研究显示亚精胺可增加*Lachnospiraceae* NK4A136的丰度,进而上调自噬相关蛋白(如LC3、Beclin1)表达并激活Toll样受体4(TLR4)介导的炎症信号通路,增强肠道屏障功能,并显著减轻饮食诱导肥胖小鼠的体重[66]。上述研究表明亚精胺对抗肥胖的核心机制在于激活自噬、改善肠道屏障功能及减轻炎症。这些系统性的改善可特异性促进白色脂肪脂解与棕色脂肪产热,最终协同控制体重并改善代谢。

3.2 亚精胺与糖尿病

一项针对16.8万英国中老年人的大型前瞻性队列研究指出,较高的饮食亚精胺和腐胺与较低的2型糖尿病风险相关,提示多胺可能成为糖尿病预防与营养干预的潜在靶点[67]。动物研究亦证实,在四氧嘧啶诱导的糖尿病大鼠中,给予亚精胺可以降低血清葡萄糖、甘油三酯和胆固醇水平[68]。糖尿病的主要特征之一是胰岛素抵抗,即机体组织细胞对胰岛素的敏感性降低,使得正常浓度的胰岛素无法产生应有的生物学效应,导致血糖水平持续升高[69]。补充亚精胺可以通过改善胰岛素抵抗显著降低糖尿病小鼠的空腹血糖并增加葡萄糖利用率[70,71]。亚精胺的乙酰化修饰可通过减轻内皮细胞损伤与炎症改善糖尿病及其并发症。亚精胺/精胺N1-乙酰转移酶SAT1缺失会导致细胞内亚精胺及其乙酰化形式减少,进而激活受体相互作用丝氨酸/苏氨酸蛋白激酶1(RIPK1)信号通路,介导细胞死亡和炎症反应[72,73]。而外源性补充亚精胺可剂量依赖性地抑制RIPK1活化,有效减少血管内皮细胞死亡,并降低多种促炎细胞因子(如TNF-α、IL-6、IL-1β)的水平[74]。胰岛β细胞数量减少亦是2型糖尿病的核心病理机制之一[75]。研究表明,在高脂饮食诱导的糖尿病小鼠模型中,亚精胺可通过增强细胞自噬有效减少胰腺β细胞死亡,从而在糖尿病进程中缓解β细胞数量的减少[76]。综上所述,亚精胺通过其激活自噬与减轻炎症的核心作用,改善胰岛素抵抗与保护β细胞功能。

3.3 亚精胺与MASLD

在高脂饮食诱导的肥胖小鼠中,亚精胺治疗可增加肝脏AMP活化蛋白激酶(AMPK)的磷酸化,进而降低下游固醇调节元件结合蛋白1c(SREBP-1c)及其靶基因脂肪酸合成酶(FAS)的表达,最终有效减轻肝脏脂肪变性和脂质积累。此外,亚精胺还能通过下调炎性细胞因子及趋化因子的表达以缓解炎症反应,并通过增强线粒体脂肪酸氧化来促进脂质消耗[77,78]。MASH患者常伴随肠道微生物组成的显著改变,而调节肠道菌群结构、丰度和功能是延缓MASH进展的关键策略。在MASH小鼠模型中补充亚精胺能够促进肠道有益菌代谢产生短链脂肪酸,有效逆转肝脂肪变性、炎症及肝纤维化的进程[79]。同时,亚精胺通过促进eIF5A的hypusine修饰,部分恢复MASH状态下线粒体蛋白表达,提升线粒体活性和脂肪酸氧化水平,从而延缓MASH发展[80]。而对已形成肝纤维化的小鼠进行为期3个月的亚精胺补充,可通过激活自噬相关蛋白MAP1S显著改善肝脏纤维化[81]。这些研究提示,亚精胺在MASLD中通过增强自噬、减轻炎症和改善线粒体功能等多条通路发挥协同作用。此外,亚精胺还通过eIF5A的hypusine修饰直接调控线粒体蛋白表达与功能,在缓解肝脏脂质积聚和纤维化中起到关键作用。

3.4 亚精胺与心血管疾病

亚精胺水平升高对高血压具有保护作用。一项双向双样本孟德尔随机化分析显示,亚精胺水平升高与高血压风险降低相关[82]。在盐敏感的大鼠中,补充亚精胺通过增强心脏自噬和有丝分裂,改善心肌细胞的机械弹性和代谢功能,最终延缓高血压性心脏病的进展[83]。在高盐饮食诱导的高血压与心

力衰竭小鼠及大鼠模型中,饮水补充亚精胺可诱导心肌细胞自噬与线粒体自噬,有效清除受损细胞,进而改善心肌细胞结构与功能、增强心肌弹性、减轻炎症反应,并最终降低血压[84]。

胆固醇代谢紊乱是心血管疾病的核心机制,低密度脂蛋白胆固醇(LDL-C)促进动脉粥样硬化,高密度脂蛋白胆固醇(HDL-C)则发挥保护作用。在动脉粥样硬化进展期的载脂蛋白E敲除($ApoE^{-/-}$)小鼠模型中,补充5 mmol/L亚精胺可有效降低LDL-C并提升HDL-C水平。此外,亚精胺还能通过刺激胆固醇外流,显著减少斑块内的坏死核心形成与脂质积聚[85]。血小板高聚集被认为是动脉粥样硬化的易感因素[86]。在饲喂高胆固醇饮食10周的新西兰兔模型中,补充10 μmol/L亚精胺可拮抗血小板聚集,表明亚精胺在高胆固醇血症引发的血小板聚集中起关键作用[87]。在老年高脂血症小鼠中,饮水补充亚精胺10周可增强线粒体自噬。这一过程通过减轻线粒体功能障碍,抑制主动脉中IL-6和线粒体自噬关键蛋白E3泛素连接酶Parkin水平的异常升高,最终抑制动脉粥样硬化形成[88]。综上,亚精胺在心血管保护中展现出多途径协同的作用机制:一方面,它通过增强心肌细胞自噬与线粒体自噬,清除受损组分,从而直接改善心脏结构与功能,延缓疾病进展;另一方面,它通过调节血脂(降低LDL-C、提升HDL-C)、抑制血小板聚集以及促进斑块内胆固醇流出,改善动脉粥样硬化。

4 总结与展望

本文总结了亚精胺与代谢性疾病的研究进展,阐明其在维持细胞稳态与代谢健康中的关键作用。亚精胺通过诱导自噬、促进eIF5A的hypusine修饰、抑制炎症和细胞凋亡以及改善线粒体功能等多种机制,协同维持机体代谢健康。亚精胺的生物学功能依赖于一个相互关联、多机制协同的调控网络,而非单一通路。然而,这一复杂网络的具体架构与整合机制尚未完全明确。作为自噬的有效诱导剂,亚精胺可能通过促进线粒体自噬,有助于恢复线粒体正常功能;功能改善的线粒体可减少活性氧的产生,并且在清除受损的线粒体后,能够减少线粒体相关损伤分子的释放,从而抑制炎症因子的产生,发挥抗炎作用;炎症水平的降低改善细胞微环境,从而进一步激活线粒体自噬,最终形成一个维持细胞稳态的良性循环。另外需要认识到,亚精胺介导的eIF5A的hypusine修饰在肿瘤中发挥着双重作用:一方面,通过增强NRF2的翻译在前列腺癌中发挥保护效应;另一方面,却促进胰腺癌的增殖与耐药。这种功能上的差异提示,亚精胺及其下游hypusine修饰具有细胞类型依赖性以及环境的特异性。在代谢性疾病中,是否也存在类似的调控差异? 例如,在代谢稳态条件下,hypusine修饰可能通过促进特定蛋白的翻译,对维持代谢稳态起到关键作用;而在持续应激状态下,其有益作用可能被异常阻断,转而发挥促炎或促纤维化作用,加剧代谢紊乱。因此,在代谢性疾病中,eIF5A的hypusine修饰所产生的最终生物学效应很可能取决于机体代谢环境的整体状态。

尤为重要的是,在衰老及多种代谢性疾病的病理状态下,体内亚精胺水平会显著下降,这使其成为一种有潜力的干预靶点或膳食补充策略。当前亚精胺的临床研究主要集中在认知障碍等衰老相关领域,针对代谢性疾病的临床研究尚未系统开展。其在改善胰岛素抵抗、缓解代谢紊乱以及减轻肝脏脂肪变性等方面的临床转化潜力,亟需更多临床试验加以验证。其次,亚精胺在人体内的最佳补充剂量、清晰的剂量-效应关系、生物利用度以及长期使用的安全性评估仍缺乏系统研究。第三,亚精胺作用机制复杂且具有潜在的双向效应。如前文所述,亚精胺在肿瘤细胞增殖与存活中扮演“双刃剑”角色。在代谢性疾病常伴发的肿瘤风险背景下,深入研究其组织特异性效应并明确其安全窗口,是推动其临床应用的重要前提。展望未来,该领域仍有许多关键科学问题有待深入探索。例如,亚精胺调控代谢的具体分子通路网络尚未完全阐明,与其他内源性多胺(如腐胺、精胺)代谢网络之间存在何种交叉调控? 长期补充亚精胺对全身免疫稳态及肠道菌群会产生怎样的系统性影响? 这些问题的解答,对于全面理解亚精胺的生物学效应至关重要。综上,未来亟需更多的基础与临床研究来深入揭示其作用机制,以期为其在代谢性疾病防治中的临床应用提供坚实的理论依据和新的策略。

参考文献

[1] Chew NWS, Ng CH, Tan DJH, et al. The global burden of metabolic disease: data from 2000 to 2019. Cell Metab, 2023, 35: 414–28.e3.

[2] Sun Z, Zheng Y. Metabolic diseases in the East Asian populations. Nat Rev Gastroenterol Hepatol, 2025, 22: 500–16.
[3] Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol, 2008, 28: 629–36.
[4] Pucciarelli S, Moreschini B, Micozzi D, et al. Spermidine and spermine are enriched in whole blood of nona/centenarians. Rejuvenation Res, 2012, 15: 590–5.
[5] Eisenberg T, Knauer H, Schauer A, et al. Induction of autophagy by spermidine promotes longevity. Nat Cell Biol, 2009, 11: 1305–14.
[6] Choi YH, Park HY. Anti-inflammatory effects of spermidine in lipopolysaccharide-stimulated BV2 microglial cells. J Biomed Sci, 2012, 19: 31.
[7] Chai N, Zheng H, Zhang H, et al. Spermidine alleviates intrauterine hypoxia-induced offspring newborn myocardial mitochondrial damage in rats by inhibiting oxidative stress and regulating mitochondrial quality control. Iran J Pharm Res, 2022, 21: e133776.
[8] Bardocz S, Duguid TJ, Brown DS, et al. The importance of dietary polyamines in cell regeneration and growth. Br J Nutr, 1995, 73: 819–28.
[9] Soda K, Kano Y, Chiba F. Food polyamine and cardiovascular disease–an epidemiological study. Glob J Health Sci, 2012, 4: 170–8.
[10] Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. Am J Clin Nutr, 2018, 108: 371–80.
[11] Lake AD, Novak P, Hardwick RN, et al. The adaptive endoplasmic reticulum stress response to lipotoxicity in progressive human nonalcoholic fatty liver disease. Toxicol Sci, 2014, 137: 26–35.
[12] Ma Y, Zhong Y, Tang W, et al. *Lactobacillus reuteri* ZJ617 attenuates metabolic syndrome via microbiota-derived spermidine. Nat Commun, 2025, 16: 877.
[13] Madeo F, Eisenberg T, Pietrocola F, et al. Spermidine in health and disease. Science, 2018, 359: eaan2788.
[14] Soda K, Kano Y, Sakuragi M, et al. Long-term oral polyamine intake increases blood polyamine concentrations. J Nutr Sci Vitaminol (Tokyo), 2009, 55: 361–6.
[15] Atiya Ali M, Poortvliet E, Stromberg R, et al. Polyamines in foods: development of a food database. Food Nutr Res, 2011, 55: 10.3402/fnr.v55i0.5572.
[16] Li B, Liang J, Baniasadi HR, et al. Functional polyamine metabolic enzymes and pathways encoded by the virosphere. Proc Natl Acad Sci U S A, 2023, 120: e2214165120.
[17] Marselli L, Bosi E, De Luca C, et al. Arginase 2 and polyamines in human pancreatic beta cells: possible role in the pathogenesis of type 2 diabetes. Int J Mol Sci, 2021, 22: 12099.
[18] Kibe R, Kurihara S, Sakai Y, et al. Upregulation of colonic luminal polyamines produced by intestinal microbiota delays senescence in mice. Sci Rep, 2014, 4: 4548.
[19] Kitada Y, Muramatsu K, Toju H, et al. Bioactive polyamine production by a novel hybrid system comprising multiple indigenous gut bacterial strategies. Sci Adv, 2018, 4: eaat0062.
[20] Matsumoto M, Sakamoto M, Benno Y. Dynamics of fecal microbiota in hospitalized elderly fed probiotic LKM512 yogurt. Microbiol Immunol, 2009, 53: 421–32.
[21] Matsumoto M, Ohishi H, Benno Y. Impact of LKM512 yogurt on improvement of intestinal environment of the elderly. FEMS Immunol Med Microbiol, 2001, 31: 181–6.
[22] Holbert CE, Cullen MT, Casero RA Jr, et al. Polyamines in cancer: integrating organismal metabolism and antitumour immunity. Nat Rev Cancer, 2022, 22: 467–80.
[23] Li J, Meng Y, Wu X, et al. Polyamines and related signaling pathways in cancer. Cancer Cell Int, 2020, 20: 539.
[24] Brito S, Heo H, Cha B, et al. A systematic exploration reveals the potential of spermidine for hypopigmentation treatment through the stabilization of melanogenesis-associated proteins. Sci Rep, 2022, 12: 14478.
[25] Takeuchi T, Harada Y, Moriyama S, et al. Vesicular polyamine transporter mediates vesicular storage and release of polyamine from mast cells. J Biol Chem, 2017, 292: 3909–18.
[26] Fredriksson R, Sreedharan S, Nordenankar K, et al. The polyamine transporter Slc18b1(VPAT) is important for both short and long time memory and for regulation of polyamine content in the brain. PLoS Genet, 2019, 15: e1008455.
[27] Madeo F, Eisenberg T, Buttner S, et al. Spermidine: a novel autophagy inducer and longevity elixir. Autophagy, 2010, 6: 160–2.
[28] Morselli E, Marino G, Bennetzen MV, et al. Spermidine and resveratrol induce autophagy by distinct pathways converging on the acetylproteome. J Cell Biol, 2011, 192: 615–29.
[29] Marino G, Morselli E, Bennetzen MV, et al. Longevity-relevant regulation of autophagy at the level of the acetylproteome. Autophagy, 2011, 7: 647–9.
[30] Gupta VK, Scheunemann L, Eisenberg T, et al. Restoring polyamines protects from age-induced memory impairment in an autophagy-dependent manner. Nat Neurosci, 2013,

16: 1453–60.

[31] Pietrocola F, Lachkar S, Enot DP, et al. Spermidine induces autophagy by inhibiting the acetyltransferase EP300. Cell Death Differ, 2015, 22: 509–16.

[32] Lee IH, Finkel T. Regulation of autophagy by the p300 acetyltransferase. J Biol Chem, 2009, 284: 6322–8.

[33] Marino G, Pietrocola F, Eisenberg T, et al. Regulation of autophagy by cytosolic acetyl-coenzyme A. Mol Cell, 2014, 53: 710–25.

[34] Mackeh R, Lorin S, Ratier A, et al. Reactive oxygen species, AMP-activated protein kinase, and the transcription cofactor p300 regulate alpha-tubulin acetyltransferase-1(alphaTAT-1/MEC-17)-dependent microtubule hyperacetylation during cell stress. J Biol Chem, 2014, 289: 11816–28.

[35] Liu P, de la Vega MR, Dodson M, et al. Spermidine confers liver protection by enhancing NRF2 signaling through a map1s-mediated noncanonical mechanism. Hepatology, 2019, 70: 372–88.

[36] Yue F, Li W, Zou J, et al. Spermidine prolongs lifespan and prevents liver fibrosis and hepatocellular carcinoma by activating MAP1S-mediated autophagy. Cancer Res, 2017, 77: 2938–51.

[37] Chrisam M, Pirozzi M, Castagnaro S, et al. Reactivation of autophagy by spermidine ameliorates the myopathic defects of collagen VI-null mice. Autophagy, 2015, 11: 2142–52.

[38] Mammucari C, Milan G, Romanello V, et al. FoxO3 controls autophagy in skeletal muscle *in vivo*. Cell Metab, 2007, 6: 458–71.

[39] 段兵兵, 王方珂, 周远飞. 亚精胺对EIF5A的hypusine修饰的生理病理功能研究进展. 生命科学, 2023, 35: 601–8.
Duan BB, Wang FK, Zhou YF. Advances in the study of spermidine via hypusine modification of EIF5A in physiopathology. Chinese Bulletin of Life Sciences, 2023, 35: 601–8.

[40] Zhang Q, Han W, Wu R, et al. Spermidine-eIF5A axis is essential for muscle stem cell activation via translational control. Cell Discov, 2024, 10: 94.

[41] Levasseur EM, Yamada K, Pineros AR, et al. Hypusine biosynthesis in beta cells links polyamine metabolism to facultative cellular proliferation to maintain glucose homeostasis. Sci Signal, 2019, 12: eaax0715.

[42] Feng D, Zhang J, Niu H, et al. Spermidine inactivates proteasome activity and enhances ferroptosis in prostate cancer. Acta Pharm Sin B, 2025, 15: 2095–113.

[43] Fujimura K, Wright T, Strnadel J, et al. A hypusine-eIF5A-PEAK1 switch regulates the pathogenesis of pancreatic cancer. Cancer Res, 2014, 74: 6671–81.

[44] Chen J, Zhu L, Cui Z, et al. Spermidine restricts neonatal inflammation via metabolic shaping of polymorphonuclear myeloid-derived suppressor cells. J Clin Invest, 2025, 135: e183559.

[45] Wang D, Yin J, Zhou Z, et al. Oral spermidine targets brown fat and skeletal muscle to mitigate diet-induced obesity and metabolic disorders. Mol Nutr Food Res, 2021, 65: e2100315.

[46] Guo X, Feng X, Yang Y, et al. Spermidine attenuates chondrocyte inflammation and cellular pyroptosis through the AhR/NF-kappaB axis and the NLRP3/caspase-1/GSDMD pathway. Front Immunol, 2024, 15: 1462777.

[47] Yang Q, Zheng C, Cao J, et al. Spermidine alleviates experimental autoimmune encephalomyelitis through inducing inhibitory macrophages. Cell Death Differ, 2016, 23: 1850–61.

[48] Noro T, Namekata K, Kimura A, et al. Spermidine promotes retinal ganglion cell survival and optic nerve regeneration in adult mice following optic nerve injury. Cell Death Dis, 2015, 6: e1720.

[49] Baek AR, Hong J, Song KS, et al. Spermidine attenuates bleomycin-induced lung fibrosis by inducing autophagy and inhibiting endoplasmic reticulum stress (ERS)-induced cell death in mice. Exp Mol Med, 2020, 52: 2034–45.

[50] Jiang D, Wang X, Zhou X, et al. Spermidine alleviating oxidative stress and apoptosis by inducing autophagy of granulosa cells in Sichuan white geese. Poult Sci, 2023, 102: 102879.

[51] Niu C, Jiang D, Guo Y, et al. Spermidine suppresses oxidative stress and ferroptosis by Nrf2/HO-1/GPX4 and Akt/FHC/ACSL4 pathway to alleviate ovarian damage. Life Sci, 2023, 332: 122109.

[52] Belle NA, Dalmolin GD, Fonini G, et al. Polyamines reduces lipid peroxidation induced by different pro-oxidant agents. Brain Res, 2004, 1008: 245–51.

[53] Rider JE, Hacker A, Mackintosh CA, et al. Spermine and spermidine mediate protection against oxidative damage caused by hydrogen peroxide. Amino Acids, 2007, 33: 231–40.

[54] Lei M, Hua X, Xiao M, et al. Impairments of astrocytes are involved in the d-galactose-induced brain aging. Biochem Biophys Res Commun, 2008, 369: 1082–7.

[55] Zhang Y, Bai J, Cui Z, et al. Polyamine metabolite spermidine rejuvenates oocyte quality by enhancing mitophagy during female reproductive aging. Nat Aging, 2023, 3: 1372–86.

[56] Singh S, Kumar R, Garg G, et al. Spermidine, a caloric restriction mimetic, provides neuroprotection against normal and D-galactose-induced oxidative stress and apoptosis through activation of autophagy in male rats during aging. Biogerontology, 2021, 22: 35–47.

[57] Liang Y, Piao C, Beuschel CB, et al. eIF5A hypusination, boosted by dietary spermidine, protects from premature brain aging and mitochondrial dysfunction. Cell Rep, 2021, 35: 108941.

[58] Schroeder S, Hofer SJ, Zimmermann A, et al. Dietary spermidine improves cognitive function. Cell Rep, 2021, 35: 108985.

[59] Camprecios G, Ruart M, Anton A, et al. Spermidine supplementation protects the liver endothelium from liver damage in mice. Nutrients, 2021, 13: 3700.

[60] Ma L, Ni Y, Hu L, et al. Spermidine ameliorates high-fat diet-induced hepatic steatosis and adipose tissue inflammation in preexisting obese mice. Life Sci, 2021, 265: 118739.

[61] Qiu C, Lu Y, Wu S, et al. Blocking adipocyte YY1 decouples thermogenesis from beneficial metabolism by promoting spermidine production. Diabetes, 2025, 74: 295–307.

[62] Ni Y, Zheng L, Zhang L, et al. Spermidine activates adipose tissue thermogenesis through autophagy and fibroblast growth factor 21. J Nutr Biochem, 2024, 125: 109569.

[63] Liao CY, Kummert OMP, Bair AM, et al. The autophagy inducer spermidine protects against metabolic dysfunction during overnutrition. J Gerontol A Biol Sci Med Sci, 2021, 76: 1714–25.

[64] Schipke J, Vital M, Schnapper-Isl A, et al. Spermidine and voluntary activity exert differential effects on sucrose- compared with fat-induced systemic changes in male mice. J Nutr, 2019, 149: 451–62.

[65] Melo NCO, Cuevas-Sierra A, Casillas-Fikentscher A, et al. Physiological responses and microbiota shifts after spermidine administration as a postbiotic on rodents fed a high-fat high-fructose diet. Benef Microbes, 2024, 15: 515–25.

[66] Ma L, Ni Y, Wang Z, et al. Spermidine improves gut barrier integrity and gut microbiota function in diet-induced obese mice. Gut Microbes, 2020, 12: 1–19.

[67] Zhang X, Qian M, Liu M, et al. The associations of dietary polyamines with incident type 2 diabetes mellitus: a large prospective cohort study. Nutrients, 2025, 17: 186.

[68] Mendez JD, Hernandez Rde H. L-arginine and polyamine administration protect beta-cells against alloxan diabetogenic effect in Sprague-Dawley rats. Biomed Pharmacother, 2005, 59: 283–9.

[69] Kjaergaard J, Stocks B, Henderson J, et al. Personalized molecular signatures of insulin resistance and type 2 diabetes. Cell, 2025, 188: 4106–22.e16.

[70] Sadasivan SK, Vasamsetti B, Singh J, et al. Exogenous administration of spermine improves glucose utilization and decreases bodyweight in mice. Eur J Pharmacol, 2014, 729: 94–9.

[71] Ma L, Zheng A, Ni L, et al. *Bifidobacterium animalis* subsp. *lactis* LKM512 attenuates obesity-associated inflammation and insulin resistance through the modification of gut microbiota in high-fat diet-induced obese mice. Mol Nutr Food Res, 2022, 66: e2100639.

[72] Shan B, Pan H, Najafov A, et al. Necroptosis in development and diseases. Genes Dev, 2018, 32: 327–40.

[73] Mifflin L, Ofengeim D, Yuan J. Receptor-interacting protein kinase 1 (RIPK1) as a therapeutic target. Nat Rev Drug Discov, 2020, 19: 553–71.

[74] Zhang T, Fu W, Zhang H, et al. Spermidine mediates acetylhypusination of RIPK1 to suppress diabetes onset and progression. Nat Cell Biol, 2024, 26: 2099–114.

[75] Walker JT, Saunders DC, Rai V, et al. Genetic risk converges on regulatory networks mediating early type 2 diabetes. Nature, 2023, 624: 621–9.

[76] Fernandez AF, Barcena C, Martinez-Garcia GG, et al. Autophagy couteracts weight gain, lipotoxicity and pancreatic beta-cell death upon hypercaloric pro-diabetic regimens. Cell Death Dis, 2017, 8: e2970.

[77] Gao M, Zhao W, Li C, et al. Spermidine ameliorates non-alcoholic fatty liver disease through regulating lipid metabolism via AMPK. Biochem Biophys Res Commun, 2018, 505: 93–8.

[78] Pankoke S, Pfarrer C, Glage S, et al. Oral supplementation with the polyamine spermidine affects hepatic but not pulmonary lipid metabolism in lean but not obese mice. Nutrients, 2022, 14: 4318.

[79] Ni Y, Hu Y, Lou X, et al. Spermidine ameliorates nonalcoholic steatohepatitis through thyroid hormone-responsive protein signaling and the gut microbiota-mediated metabolism of bile acids. J Agric Food Chem, 2022, 70: 6478–92.

[80] Zhou J, Pang J, Tripathi M, et al. Spermidine-mediated hypusination of translation factor EIF5A improves mitochondrial fatty acid oxidation and prevents non-alcoholic steatohepatitis progression. Nat Commun, 2022, 13: 5202.

[81] Shi B, Wang W, Ye M, et al. Spermidine suppresses the

activation of hepatic stellate cells to cure liver fibrosis through autophagy activator MAP1S. Liver Int, 2023, 43: 1307–19.

[82] Wang T, Li N, Zeng Y. Protective effects of spermidine levels against cardiovascular risk factors: an exploration of causality based on a bi-directional Mendelian randomization analysis. Nutrition, 2024, 127: 112549.

[83] Eisenberg T, Abdellatif M, Zimmermann A, et al. Dietary spermidine for lowering high blood pressure. Autophagy, 2017, 13: 767–9.

[84] Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat Med, 2016, 22: 1428–38.

[85] Michiels CF, Kurdi A, Timmermans JP, et al. Spermidine reduces lipid accumulation and necrotic core formation in atherosclerotic plaques via induction of autophagy. Atherosclerosis, 2016, 251: 319–27.

[86] Ross R. The pathogenesis of atherosclerosis–an update. N Engl J Med, 1986, 314: 488–500.

[87] de la Pena NC, Sosa-Melgarejo JA, Ramos RR, et al. Inhibition of platelet aggregation by putrescine, spermidine, and spermine in hypercholesterolemic rabbits. Arch Med Res, 2000, 31: 546–50.

[88] Tyrrell DJ, Blin MG, Song J, et al. Age-associated mitochondrial dysfunction accelerates atherogenesis. Circ Res, 2020, 126: 298–314.