Pharmacy Information 药物资讯, 2024, 13(4), 355-361
Published Online July 2024 in Hans. https://www.hanspub.org/journal/pi
https://doi.org/10.12677/pi.2024.134041

Hans汉斯

血管活性肽在自身免疫性疾病发生发展中的参与及作用

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收稿日期：2024年6月4日；录用日期：2024年7月8日；发布日期：2024年7月16日

摘　要

血管活性肠肽(vasoactive intestinal peptide, VIP)是一种主要存在于中枢神经系统和肠道神经系统的神经递质，在肠道神经系统主要由肠神经元释放，既是一种胃肠激素，又是一种具有多种功能的神经肽。VIP对多种自身免疫性疾病具有治疗潜力，包括类风湿性关节炎、炎症性肠病和干燥综合征等。本文总结VIP在多种自身免疫性疾病发生发展中的参与及作用，为上述疾病的治疗提供新思路。

关键词

血管活性肠肽，自身免疫性疾病，作用机制

The Involvement and Role of Vasoactive Peptides in the Occurrence and Development of Autoimmune Diseases

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Received: Jun. 4th, 2024; accepted: Jul. 8th, 2024; published: Jul. 16th, 2024

Abstract

Vasoactive intestinal peptide (VIP) is a neurotransmitter primarily found in the central nervous system and the enteric nervous system. In the enteric nervous system, it is predominantly re-

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文章引用: 李佳琳, 戴岳. 血管活性肽在自身免疫性疾病发生发展中的参与及作用[J]. 药物资讯, 2024, 13(4): 355-361.
DOI: 10.12677/pi.2024.134041

leased by enteric neurons. It serves as both a gastrointestinal hormone and a neuropeptide with various functions. VIP holds therapeutic potential for several autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, and Sjögren's syndrome. This article summarizes the involvement and effects of VIP in the occurrence and development of multiple autoimmune diseases, providing new insights for the treatment of the aforementioned conditions.

Keywords

Vasoactive Intestinal Peptide, Autoimmune Diseases, Mechanism of Action

1. 引言

1969 年，人们首次发现在哺乳动物肺部存在一种具有血管扩张能力的肽类物质，并从猪的十二指肠组织中成功分离出这种多肽，因可以扩张血管，将其命名为血管活性肠肽(Vasoactive intestinal peptide, VIP) [1]。VIP 是一种由 28 个氨基酸组成的多肽，主要与三种受体结合，分别为 VIP 受体 1 (VPAC1)、VIP 受体 2 (VPAC2)和 PACAP 受体 1 (PACAPR1)，广泛存在于中枢神经系统和胃肠道神经系统[2]。

自身免疫性疾病是指机体的免疫系统错误地攻击和破坏正常组织和器官，导致炎症和组织损伤的一类疾病。多种神经肽在自身免疫性疾病的发生发展中具有重要作用。生长抑素(Somatostatin, SOM)可抑制类风湿性关节炎(Rheumatoid arthritis, RA)发展，临床研究表明 SOM 类似物奥曲肽可明显改善类风湿性关节炎患者的临床症状[3]；皮质抑素(Cortistatin, CST)可显著改善 2，4，6-三硝基苯磺酸溶液(2, 4, 6-trinitrobenzenesulfonic acid solution, TNBS)诱导的结肠炎小鼠的疾病症状[4]；神经肽 Y (Neuropeptide Y, NPY)RA 患者滑膜中 NPY 水平降低，并且与关节炎疾病严重程度呈负相关；同时 NPY 还可以发挥抗炎作用并参与固有免疫和适应性免疫调节[5]。本文总结 VIP 在自身免疫性疾病发生发展中的表达变化以及其对疾病的改善作用。

2. VIP 在自身免疫性疾病发生发展中的参与及作用

2.1. 类风湿性关节炎

RA 是一种慢性炎症性自身免疫疾病。主要病理特征为关节滑膜的慢性炎症、血管翳形成和软骨破坏，最终导致不可逆的关节强直畸形和功能丧失[6]。临床表现为对称性、持续性的关节肿痛、畸形，伴有晨僵、乏力，并累及全身多器官[7]。

早期 RA 患者血清中 VIP 水平很低，且血清 VIP 水平与疾病严重程度呈负相关，提示 VIP 可作为早期 RA 患者的预后指标，即患者血清中 VIP 水平越低，预后越差[8]。在 RA 动物模型的研究中，胶原诱导的关节炎(collagen-induced arthritis, CIA)模型与人类 RA 的病情发展和临床表现相似，是目前公认的 RA 最佳模型[9]。

CIA 小鼠腹腔注射 VIP 能够降低关节炎的发生率，减轻关节组织中炎性细胞浸润和软骨破坏，降低血清中 IFN-γ 水平，升高 IL-4 水平[10]。类似地，VIP 降低 CIA 大鼠踝关节炎性细胞浸润，减轻骨损伤和骨破坏，降低血清中 TNF-α 和 IL-2 水平，升高 IL-4 水平[11]。

VIP 可显著抑制 TNF-α 诱导的 RA 患者滑膜组织成纤维细胞 IL-6 表达[12]，抑制 RA 患者外周血淋巴细胞中 TNF-α 和 IL-6 细胞因子表达，下调 CXCL8 和 CCL2 趋化因子的表达[13]。此外，VIP 能够使 RA 患者滑膜中巨噬细胞从促炎表型转为抗炎表型[14]。VIP 还可抑制 CIA 小鼠骨髓来源的破骨细胞的增殖，调节 CIA 小鼠脾脏淋巴细胞中 Treg/Th17 细胞平衡，减轻踝关节骨损伤和骨破坏[15]。

RA 患者血清中 VIP 水平与疾病发展密切相关，VIP 可改善 RA 的疾病症状，其机制与抑制促炎因子的释放和调节 T 细胞平衡有关。

2.2. 炎症性肠病

炎症性肠病(inflammatory bowel disease, IBD)是一种非特异性的慢性肠道炎性疾病，主要包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(crohn′s disease, CD)。UC 是一种主要累及直肠、结肠黏膜及黏膜下层的慢性炎症性疾病，CD 的病变部位可累及全消化道，一般呈节段性分布，病程多反复发作，迁延不愈，主要临床表现为腹痛、腹泻、肠梗阻，可伴有发热、营养障碍等肠外症状[16]。

IBD 患者的肠道中含 VIP 的神经纤维丰度与健康人群相比明显降低，且神经纤维丰度下降的变化与疾病的严重程度呈正相关[17]。与健康人群相比，IBD 患者血清中 VIP 含量也明显降低[18]。

在葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)诱导的小鼠结肠炎模型中，VIP 敲除小鼠比野生型小鼠的疾病症状更严重，补充 VIP 后减轻小鼠疾病症状。此外，VIP 还能维持结肠上皮屏障结构，促进结肠炎期间的上皮屏障修复，维持肠屏障稳态[19]。在 TNBS 诱导的小鼠结肠炎模型中，腹腔注射 VIP 可显著改善小鼠体重减轻、腹泻以及肠道炎性细胞浸润等疾病症状，降低结肠组织髓过氧化物酶活性，下调 GPR35 受体表达，减少中性粒细胞募集。此外，VIP 能够降低 TNBS 诱导的结肠炎小鼠肠系膜淋巴结中 IL-17 mRNA 表达，促进 Foxp3 和 IL-10 mRNA 表达，调节 Th17/Treg 细胞平衡[20]。VIP 在其他结肠炎模型中也表现出对疾病的改善作用，例如啮齿类枸橼酸杆菌诱导的结肠炎[21]。从 TNBS 诱导的结肠炎小鼠的脾脏组织中分离原代淋巴细胞和固有层免疫细胞，VIP 降低细胞中细胞因子 IFN-γ 和 TNF-α 水平，上调 IL-4 和 IL-10 水平，调节 Th1/Th2 细胞平衡[22]。

IBD 患者肠道中 VIP 的神经纤维丰度和血清中 VIP 水平较健康志愿者相比明显降低，VIP 敲除小鼠表现出疾病加重。VIP 对多种动物模型均有改善作用，其机制与维持肠屏障稳态、抑制促炎因子释放和调节 T 细胞平衡有关。

2.3. 干燥综合征

干燥综合征(sjogren’s syndrom, SS)是一种累及唾液腺、泪腺等外分泌腺和其他器官的慢性炎症性自身免疫性疾病，临床表现除有唾液腺和泪腺受损功能下降而出现口干、眼干外，尚有多系统损害的症状[23]。

与健康人群相比，SS 患者在唾液腺泡和唾液管中含 VIP 的神经纤维缺失，且在患者唾液萎缩腺泡中 VIP 的结合位点消失[24]。因其病理机制尚不明确，多种动物模型被用来研究 SS 的病理过程。其中非肥胖糖尿病(non-obese diabetes, NOD)小鼠模型被认为是目前比较贴合 SS 的动物模型[25]。与正常小鼠相比，NOD 小鼠下颌下腺中 VIP 的表达降低，且与疾病严重程度呈正相关[26]。对 NOD 小鼠腹腔注射 VIP 能够降低外分泌腺中 IL-17A 的水平，改善外分泌腺的病变并恢复腺体的分泌功能[27]。在 NOD 小鼠下颌下腺滴注编码人 VIP 转基因的载体重组血清型 2 腺相关病毒后，下颌下腺和血清中 VIP 表达增加，唾液流速升高，疾病症状得到明显改善[28]。此外，对 NOD 小鼠腹腔注射 VIP 后，小鼠下颌下腺淋巴细胞浸润明显减轻，饮水量减少。从 NOD 小鼠的脾脏组织中分离原代淋巴细胞，外源给予 VIP 后使 Treg 细胞比例增加，Th17 细胞比例减少[29]。

与健康志愿者相比，SS 患者表现出病灶处神经纤维缺失。VIP 可以显著改善 NOD 小鼠疾病症状，

其机制与抑制促炎细胞因子释放、减轻炎性细胞浸润和 T 细胞平衡有关。

2.4. 多发性硬化症

多发性硬化症(multiple sclerosis, MS)是一种中枢神经系统慢性炎性脱髓鞘性疾病，免疫系统在疾病的发生发展中具有重要作用。神经纤维外包裹有髓鞘，免疫系统错误地攻击髓鞘，导致神经功能受损，影响神经信号的正常传递，出现疾病症状。MS 常累及大脑、脊髓白质、皮质下结构、脑干、小脑和视神经，如果不进行及时有效的治疗，最终可导致患者肌肉协调性丧失，视功能丧失[30]。

MS 患者血清中 VIP 水平较健康人群明显降低[31]，且脑脊液中 VIP 水平与健康人群相比同样呈降低的趋势[32]。MOG 是一种只存在于髓鞘膜和髓磷脂少突胶质细胞表面的糖蛋白，属于免疫球蛋白超家族，具有免疫源性高、可诱导产生抗 MOG T 淋巴细胞等特点。MOG 可诱发复发、实验性自身免疫性脑脊髓炎(experimental autoimmune encephalomyelitis, EAE)。使用同种异体间充质干细胞(MSCs)为载体，将 VIP 输送到 EAE 小鼠的中枢神经系统，可通过改善炎症、减轻外周 T 细胞对 MOG 的反应和提高脱髓鞘与神经元的完整性改善疾病症状，并阻止疾病发展[33]。此外，对 EAE 小鼠腹腔注射 VIP 可增加神经系统 Treg 细胞比例，抑制 Th17 细胞活化，降低 IFN-γ、IL-6 和 IL-2 等细胞因子以及 RANTES、MCP-1 和 MIP-1α 等趋化因子表达[34]。

MS 患者血清中 VIP 水平降低，VIP 可显著改善 EAE 小鼠疾病症状，其机制与抑制促炎细胞因子释放和调节 T 细胞平衡有关。

2.5. 其他

I 型糖尿病(type 1 diabetes mellitus, T1DM)是一种由 T 细胞介导的自身免疫性疾病，免疫系统错误的攻击胰腺中产生胰岛素的细胞，导致胰岛素缺乏，引起血糖升高[35]。在 NOD 小鼠模型中，VIP 抑制 NOD 小鼠血清中促炎因子释放，减轻胰腺中 β 细胞损伤[36]，VIP 敲除小鼠血浆中葡萄糖水平升高[37]。过表达 NOD 小鼠的 VIP 基因后，胰腺 β 细胞中胰岛素分泌增加，NOD 小鼠的葡萄糖耐受不良得到改善[38]。系统性红斑狼疮(systemic lupus erythematosus, SLE)是一种多发于青年女性的累及多脏器的自身免疫性炎症性结缔组织疾病[39]。VIP 能够显著降低模型小鼠外周血和脾脏组织淋巴细胞中 IL-17 和 IL-6 的 mRNA 和蛋白水平，上调 Foxp3 和 IL-10 的 mRNA 和蛋白水平，抑制 Th17 细胞分化，促进 Treg 细胞的生成，从而恢复 Th17/Treg 细胞平衡，改善小鼠疾病症状[40]。

3. 总结与展望

VIP 的商品名为 Aviptadil，已在临床上成功用于肺动脉高压和结节病的治疗。然而，VIP 在临床中发挥的治疗作用远远不及预期。主要原因包括：1) 靶向性差，能够与不同的 GCPR 结合，易引起不良反应；2) 易被蛋白酶降解[41]。针对 VIP 临床应用存在的问题，已经提出一些针对性策略，包括：1) 使用金属纳米颗粒作为 VIP 的载体，加强 VIP 的靶向性[42]；2) 使用修饰过的脂质体或纳米胶束与 VIP 结合，减少其在体内的降解[43]；3) 开发稳定的 VPAC1 和 VPAC2 受体类似物，如 LBT-3627 [44]。

VIP 或其受体的差异表达体现在许多自身免疫性疾病的发病进程中。在早期 RA 患者和活动期 RA 患者的外周血单核细胞(PBMC)中，VPAC1 表达降低[45]，VPAC2 在 MS 患者活化的 CD4 + T 细胞中表达降低[46]。VIP 能否作为自身免疫性疾病的生物标志物，靶向 VIP 或其受体能否有效防止相关疾病值得深入研究。

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