

5型磷酸二酯酶抑制剂在治疗下尿路功能障碍中的应用

PHOSPHODIESTERASE TYPE 5 INHIBITORS IN TREATMENT OF LOWER URINARY TRACT DYSFUNCTIONS

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本文综述了近年来选择性应用5型磷酸二酯酶抑制剂治疗下尿路症状的药理学和病原基础的研究进展。详细探讨了这些药物对各种尿路功能障碍的治疗作用机制，其中以改善血液循环、降低盆腔器官缺血为主导。

关键词：5型磷酸二酯酶抑制剂；下尿路功能障碍；盆腔器官缺血；他达拉非

The article provides a review of current data on the pharmacological and pathogenetic principles of the use of selective type 5 PDE inhibitors in patients with lower urinary tract dysfunctions. The mechanisms of the therapeutic action of these drugs for various urinary tract dysfunctions are examined in detail, the leading of which is the improvement of blood circulation and the reduction of ischemia of the pelvic organs.

Keywords: phosphodiesterase type 5 inhibitors; lower urinary tract dysfunctions; ischemia of the pelvic organs; tadalafil.

5型磷酸二酯酶抑制剂 (PDE5i-) 已被证明是改善血管内皮功能障碍进程和延缓其进展的有效药物。在泌尿外科实践中, PDE5i 广泛用于勃起功能障碍 (ED) 的治疗。与此同时, 鉴于PDE5i的生理和临床效应的多样性-, 对其应用新领域的探索仍在继续。应用PDE5i为了治疗下尿路功能障碍是有前途的。

首次当观察到ED患者排尿改善时, PDE5i-有了新的潜在应用。关于这一主题的第一份报告发表于2002年[1], 并引发了这方面的深入研究。流行病学研究结果证实ED的发生与下尿路症状 (LUTS) 密切相关。结果发现, ED患者中下尿路症状的患病率为72.2%, 无ED一仅为37.7%[2]。俄罗斯一项对1225名年龄在22岁至70岁之间的男性进行的研究也得出了类似的结果[3]。进一步的研究表明, 除了ED和下尿路症状的高患病率外, 还有共同的危险因素。其中之一是代谢综合征, 临床表现为糖尿病、动脉性高血压、肥胖[4-6]。

大多数研究者认为盆腔缺血是盆腔功能障碍发生的主要致病原因因素。对于LUTS和ED, 这是完全正确的。其发育过程主要有四种常见的病理生理机制: 盆腔器官一氧化氮 (NO) 合成减少, 交感神经系统过度亢进, 视激酶酶活性增加, 盆腔血管粥样硬化[7,8]。

1、一氧化氮合成的下降。一氧化氮在勃起功能中的作用是众所周知的。血管平滑肌细胞内的内皮同种型NO激活鸟苷酸环化酶, 其增加了环鸟苷酸 (cGMP) 的产生, 并通过一系列的反应导致细胞内钙含量下降, 海绵体肌细胞的松弛。因此, NO合成的减少伴随着勃起功能的破坏。在尿路中, NO的缺乏导致膀胱和尿道平滑肌细胞的张力增加, 并增加其传入活动[9,10]。临床表现为膀胱过度活跃。

2、交感神经系统的过度活跃。实验和临床研究表明, 下尿路和ED功能障碍与动脉高血压相关, 而动脉高血压与交感神经系统活动增强

密切相关[11,12]。动脉性高血压与高血糖、肥胖、高脂血症是代谢综合征的组成部分之一，其与ED、下尿路症状的关系已被众多研究证实[4,5]。

3、激酶活性的增加。激酶的酶供养 Ca^{2+} ，即是独立平滑肌细胞的收缩机制[13]。在内皮细胞中，涉及激酶的级联反应导致NO活性降低，从而阻止平滑肌松弛，并促进ED和下尿路症状的发展[14]。激酶活性的增加在糖尿病和动脉高血压患者中观察到的[15]。在这方面，激酶活性的增加被认为是ED与下尿路症状之间的结合机制之一[16]。

4、盆腔血管粥样硬化。动脉粥样硬化性血管病变导致血流受损和盆腔缺血，导致ED和下尿路症状的出现[17]。本实验表明，膀胱血管粥样硬化病变同时伴有其壁的弹性和延展性下降[18]。多普勒造影发现动脉粥样硬化性血管病变较明显时，膀胱容量较小，排尿频率增加[19]。盆腔器官缺血时，膀胱充盈时，出现血流动力学参数的下降，而排空后，血液再灌注可引起细胞氧化损伤。再灌注损伤在膀胱内血管粥样硬化患者中尤为明显[20]。

因此，盆骨血流异常导致下尿路缺血被认为是下尿路功能障碍发生的主要致病因素。盆腔缺血，伴膀胱颈梗阻和神经系统疾病，已被证明是下尿路症状发生的独立危险因素，特别是膀胱过度活跃[21-23]。膀胱过度活跃是一种广泛存在的疾病，严重影响患者的生活质量[24,25]。The First Pavlov State Medical University of St. Petersburg的泌尿外科诊所研究了膀胱过度活跃患者膀胱壁微循环的状态[26,27]。研究结果表明，微循环障碍的严重程度与疾病症状的严重程度相关。在这种情况下，动脉血流量的恶化程度与迫切的排尿冲动的严重程度相关，而静脉和毛细血管血流量的紊乱程度与排尿频率相关。膀胱壁微循环障碍的严重程度取决于盆腔器官脱垂的程度，并与动脉高血压、冠心病和慢性便秘的存在相关。所获得的数据使我们得出结论，对于膀胱过度活跃的患者，使用改善膀胱壁微循环状态的药物是合适的[26,27]。

R.T. Kershen等人的[28]研究表明，随着膀胱充盈，膀胱壁的血流变差，这是由于腔内血管受压所致，排空膀胱后，血流增加。急性尿潴留，由于膀胱内压力增加而使壁内血管受到机械压迫，引起持续性血管痉挛和逼尿肌缺血，从而导致膀胱功能障碍[29]。R. Vince等人[30]的实验研究证实，随着充盈期膀胱内压的增加，膀胱灌注减少。所得结果具有重要的临床意义。膀胱逼尿肌亢进时膀胱的不自主收缩活动、膀胱内压力在膀胱颈梗阻中的增加、减少膀胱壁纤维化时的可扩展性会导致膀胱壁血流的恶化。随着缺血背景下逼尿肌形态的改变，出现壁内神经的损伤，其导致逼尿肌去神经化，甚至更严重地破坏膀胱的功能。因此，膀胱壁缺血是膀胱首次过度活动的主要发病机制，然后随着形态学改变的增加和逼尿肌失代偿，向功能障碍的状态。在早期对糖尿病合并糖尿病性膀胱病患者尿路结构和功能变化的研究中也发现了类似的变化序列[31-33]。

由于ED和下尿路症状具有共同的发病机制，所以有理由期望治疗方法也应该是类似的。在这方面，PDE5i的采用完全符合这一概念。PDE5在下尿路症状-中有效的主要治疗机制是逼尿肌和尿道平滑肌的放松和下尿路血流的改善。这两种效应都与PDEi的治疗作用机制有关。这些药物会阻断PDE5-酶，其存在于膀胱、尿道、前列腺和血管壁的平滑肌细胞中。PDE5-帮助环鸟苷酸转化为鸟苷三磷酸，其导致蛋白激酶G的活性降低，NO介导信号的终止，增加细胞内钙的浓度，降低钾浓度，肌动蛋白和肌球蛋白的磷酸化，从而导致尿路平滑肌细胞减少和血管收缩[34]。因此，PDE5i-通过增加平滑肌细胞中环鸟苷酸的浓度，降低下尿路的张力，促进壁内血管扩张，这两种作用都能改善盆腔器官的血流[35,36]。在实验中发现，PDE5-抑制剂也能抑制激酶活性，有助于减轻膀胱壁缺血的严重程度[37]。改善膀胱壁血液灌注的另一可能机制是改善水泡动脉的血流。研究发现，该动脉具有PDE5-的高活性，其由他达拉非抑制的[36]。PDEI5型治疗效果的一个重要方面是调节膀胱感觉功能的能力。在实验中，发现了PDE5i-不仅减少

A δ 机械敏感性的传入活动,也减少C纤维的机械敏感性的传入活动,这在治疗膀胱血脑屏障异常活跃的患者中尤为重要[38]。

因此,使用PDE抑制剂治疗下尿路功能障碍似乎在药理和病原上是合理的[10,21]。目前已知的PDE酶有几种类型,其中一些主要水解环腺苷单磷酸,另一些一环鸟苷酸。在膀胱组织中发现PDE类型1A、1B、2A、4A、4B、5A、7A、8A、9A的RNA信使,其中大部分抑制下尿路症状的裂解[39]。PDE5型抑制剂在临床实践中的应用已成为最广泛的。通过免疫组化研究和定量聚合酶链反应对mRNA表达进行评价,发现PDE5-酶存在于膀胱、尿道和前列腺的肌纤维和血管中,此外,在膀胱中检测到了最高的浓度,而最低的在前列腺中[40]。

大量的实验和临床研究结果证实了PDE5i-的有效性。实验显示了PDE5i-能够减少膀胱的收缩活动和减少膀胱的传入活动在脊髓损伤导致膀胱神经源性活动过度的动物中[41]。实验也为PDE5-抑制剂改善膀胱血流量的能力提供了证据[42]。

临床研究结果证实了PDE5i-无论是作为单一治疗还是与其他药物联合使用对下尿路症状的治疗效果[43-46]。因此,当他达拉非规定每天5毫克的剂量,从治疗第一周开始,PDE5i-的症状有所改善,其表现为IPSS问卷得分显著下降22-37%[45]。结果发现,与安慰剂相比,PDE5i-可显著改善IPSS(国际前列腺评分表)和IIEF(国际勃起功能指数)的指标,对最大尿流率无显著影响[46-48]。PDE5i-的一个重要的临床应用领域是与其他药物联合使用。五项随机临床试验的荟萃分析结果表明了(在两项研究中,他达拉非的剂量为20毫克,在两项研究中一西地那非为25毫克,在一项研究中一伐地那非为20毫克),联合治疗与 α -受体阻滞剂单药治疗相比显著改善了IPSS(-1.8)和IIEF(+3.6)问卷的表现,并增加尿液的最大流量(+1.5毫升/秒)[49]。

A.V. Sivkov等人[50]的报告显示了一些研究的结果,该研究比较了PDE5i-伐地那非(20 mg /天)

和索利那新的M抗胆碱(5 mg/天)对膀胱过度活跃和ED男性患者疗效的有效性。治疗时间为8周。所有接受治疗的患者都报告病情有所好转。在接受伐地那非治疗的26例患者中,4例显示了完全消失了膀胱过度活跃的症状。本组患者尿动力学指标阳性。治疗后,第一次非随意性逼尿肌收缩(IDC)发生时,膀胱平均充盈量显著增加,从 93.9 ± 14.4 到 146.4 ± 13 cm H₂O, IDC降到了从 2.5 ± 1.1 到 1.9 ± 0.9 ,最大IDC幅度降到了从 21.1 ± 10 到 15.3 ± 9.4 cm H₂O,最大膀胱容量增加了从 150.2 ± 31.5 到 224.7 ± 40.1 ml。在服用索利那新后,所有患者均报告病情有所改善,治疗效果在减少尿频、紧急冲动和紧急尿失禁发作方面更为显著。作者的结论是,将PDE5i-作为单一疗法或联合疗法的一部分给膀胱过度活跃患者是合适的[50]。

在良性前列腺增生患者中,PDE5i-被认为是一种发病的治疗。良性前列腺增生背景下下尿路症状对男性的治疗作用机制主要有:前列腺和膀胱肌张力降低;前列腺内氧合和灌注增加;前列腺增生减少;前列腺炎症的减少和膀胱传入活动的抑制[51,52]。

PDE5i-的使用在治疗膀胱功能障碍的患者中具有病理上的合理性。临床表现为排尿困难,无排尿或排尿冲动明显减弱,残余尿量增加。在某些情况下,独立排尿可能不存在[53]。尿动力学检查显示逼尿肌收缩活性下降,并膀胱敏感性下降。膀胱功能障碍的原因是多种多样的。它通常是神经系统疾病的并发症(周围神经病,腰骶脊髓损伤),由于膀胱失代偿在膀胱颈梗阻的病人,以及在一些疾病,直接导致膀胱血管的损伤,如糖尿病。与此同时,无论病因如何,膀胱壁缺血在某些情况下对膀胱功能障碍的发生发展起着重要的决定作用。因此,膀胱壁缺氧伴随着壁内神经末梢的丢失(膀胱失神经),平滑肌细胞功能的下降,胶原纤维的生长,往往使这种情况不可逆转[53,54]。

有一种单独形式的膀胱功能障碍—逼尿肌过度活动伴收缩功能受损。许多研究人员认为这是一种从过度活跃到逼尿功能障碍的状

态[55]。该状态为膀胱功能障碍来临床表现(增加排尿, 紧急冲动及紧急尿失禁), 虽然有排尿困难和残余尿量增加, 即在排空阶段, 逼尿肌不能完全发挥其功能。在一项实验中研究了这种情况, 并在神经系统疾病、膀胱颈梗阻和糖尿病中进行了描述[55–57]。这种情况的进一步发展导致《纯》膀胱功能障碍。

D.Gotoh等人[58]对糖尿病细胞病的实验模型, 其膀胱功能障碍显示的, 研究了他达拉非对膀胱血流的影响。动物接受他达拉非, 每日2毫克/公斤, 连续7天。PDE5i-的服用有助于改善膀胱壁微循环的指标, 这给了作者一个理由指出开iPDE5i-药为了改善膀胱血流量的前景[58]。在另一项使用神经源性膀胱功能障碍模型的实验研究中, 研究表明膀胱内血液流动的改善有助于逼尿肌收缩、膀胱容量的减少和残余尿量的增加[59]。

以膀胱功能障碍的情况下, 改善膀胱排空是治疗的主要目标。这个任务既可以通过增加逼尿肌的收缩活动, 又通过降低膀胱出口阻力来完成。由于膀胱出口区平滑肌细胞的松弛是由氮氧化物介导的, 因此在这类患者中采用PDE5i-也可能有治疗效果。在最近发表的一篇文章中, 这个概念在实验中得到了证实[60]。神经源性膀胱功能障碍与逼尿肌一括约肌肌痛联合模型显示了, 他达拉非的应用显著减少了残余尿量, 提高了排尿效率, 而逼尿肌的收缩活动没有增加。因此, 在排空过程中, 通过增加尿道的松弛来达到治疗的效果, 从而提高了排空的效率[60]。

因此, 下尿路功能障碍的患者中应用PDE5i-是具有病原意义的, 并所进行的研究显示了它们的临床有效性。迄今为止, 由 European Association of Urology 推荐并经FDA批准用于下尿路症状治疗唯一的PDE5i-是他达拉非。在临床研究中, 已证明了有效的治疗尿路功能障碍和其他PDE5i-用于治疗ED。除他达拉非外, 目前有6种口服的PDE5i-, 即西地那非、伐地那非、阿伐那非、乌地那非和米罗地那非。考虑到一般药理特性, 有理由相信, 它们在治疗下尿路症状方面也将是有效的。

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