doi: 10.13241/j.cnki.pmb.2022.07.004

布地奈德混悬液对哮喘幼鼠上皮 - 间充质转化和气道重塑的影响及机制 *

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摘要 目的：探讨布地奈德混悬液对哮喘幼鼠上皮 - 间充质转化和气道重塑的影响及机制。**方法：**将哮喘幼鼠(n=36)随机平分为三组 - 模型组、布地奈德 1 组、布地奈德 2 组，三组分别给予雾化吸入生理盐水、布地奈德混悬液 0.1 mg 与布地奈德混悬液 0.2 mg，1 次 /d，共 14d，检测与观察幼鼠上皮 - 间充质转化和气道重塑变化情况。**结果：**布地奈德 1 组、布地奈德 2 组的支气管肺泡灌洗液白细胞总数与嗜酸性粒细胞总数都低于模型组(P<0.05)，布地奈德 2 组低于布地奈德 1 组(P<0.05)。布地奈德 1 组、布地奈德 2 组的血清肿瘤坏死因子(Tumor necrosis factor，TNF)-α、血红素加氧酶(heme oxygenase，HO)-1 含量低于模型组(P<0.05)，布地奈德 2 组低于布地奈德 1 组(P<0.05)。布地奈德 1 组、布地奈德 2 组的支气管壁厚度(WAt/Pi)、支气管壁平滑肌细胞核数量(N/Pi)、支气管壁平滑肌厚度 (WAm/Pi) 都高于模型组，布地奈德 2 组高于布地奈德 1 组 (P<0.05)。布地奈德 1 组、布地奈德 2 组的肺组织 E-cadherin、NF-κB 蛋白相对表达水平低于模型组(P<0.05)，布地奈德 2 组低于布地奈德 1 组(P<0.05)。**结论：**布地奈德混悬液在哮喘幼鼠的应用能抑制上皮 - 间充质转化和气道重塑，也可抑制 TNF-α、HO-1 的释放，减轻嗜酸性粒细胞与白细胞的浸润，从而发挥肺保护作用，且存在剂量依赖性。

关键词：布地奈德混悬液；哮喘；幼鼠；上皮 - 间充质转化；气道重塑；肿瘤坏死因子 -α；血红素加氧酶 -1

中图分类号：R-33；R562.25 **文献标识码：**A **文章编号：**1673-6273(2022)07-1216-04

Effect and Mechanism of Budesonide Suspension on Epithelial-mesenchymal Transition and Airway Remodeling in Asthmatic Young Mice*

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ABSTRACT Objective: To investigate the effects and mechanism of budesonide suspension on epithelial-mesenchymal transition and airway remodeling in asthmatic young rats. **Methods:** Asthmatic infant rats (n=36) were randomly divided into three groups-model group, budesonide 1 group, and budesonide 2 groups. The three groups were given aerosol inhalation of normal saline, budesonide suspension 0.1 mg, budesonide suspension 0.2 mg, 1 time/d, for a total of 14 days, detected and observed the changes of epithelial-mesenchymal transition and airway remodeling in the rats. **Results:** The total number of leukocytes and eosinophils in the bronchoalveolar lavage fluid of the budesonide group 1 and budesonide group 2 were lower than those of the model group (P<0.05), and the budesonide group 2 were lower than the budesonide group 1 (P<0.05). The serum tumor necrosis factor (TNF)-α and heme oxygenase (HO)-1 levels in budesonide group 1 and budesonide group 2 were lower than those in the model group (P<0.05), and the budesonide group 2 were lower than budesonide group 1 (P<0.05). The bronchial wall thickness (WAt/Pi), the number of bronchial wall smooth muscle cell nuclei (N/Pi) and the bronchial wall smooth muscle thickness (WAm/Pi) of the budesonide group 1 and budesonide group 2 were higher than those of the model group, and the budesonide group 2 were higher than the budesonide group 1 (P<0.05). The relative expression levels of E-cadherin and NF-κB protein in lung tissues of budesonide group 1 and budesonide group 2 were lower than those of the model group (P<0.05), and budesonide group 2 were lower than budesonide group 1 (P<0.05). **Conclusion:** The application of budesonide suspension in asthmatic young mice can inhibit epithelial-mesenchymal transition and airway remodeling, and can also inhibit the release of TNF-α and HO-1, and reduce the infiltration of acidic granulocytes and leukocytes, thereby reduce the infiltration of acidic granulocytes and leukocytes. So as to play lung protective effect, and there are dose-dependent.

Key words: Budesonide suspension; asthma; Young mice; Epithelial-mesenchymal transition; Airway remodeling; Tumor necrosis factor-α; Heme oxygenase-1

Chinese Library Classification(CLC): R-33; R562.25 Document code: A

Article ID:1673-6273(2022)07-1216-04

* 基金项目：陕西省国际科技合作计划项目（2018KW-041）

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（收稿日期：2021-07-23 接受日期：2021-08-18）

前言

哮喘是儿童时期最常见的慢性呼吸道过敏性疾病，以反复发作的气促、胸闷、喘息、咳嗽等为主要临床表现，常在夜间出现症状加剧，导致患儿出现气道不可逆性缩窄和气道重塑[1,2]。近年来哮喘在儿童群体中发病率逐年增加，特别是1-3岁儿童的患病率最高[3]。研究显示：上皮-间充质转化和气道重塑是哮喘发生的基础，Th1/Th2细胞失衡是造成哮喘的免疫学基础[4,5]。如能上调Th1细胞的表达，抑制Th2细胞的表达，使Th1/Th2恢复平衡状态，即可发挥对哮喘的治疗作用[6]。最新研究表明，气道炎症、过敏反应引发细胞因子网络紊乱以及微肠道微生物等均与慢性呼吸道过敏性疾病关系密切[7,8]。目前哮喘药物包括控制性药物和缓解性药物，其中糖皮质激素是临床应用最为广泛的甾体类抗炎药物，能有效减轻哮喘患儿的气道阻塞，降低气道高反应性，能快速发挥缓解作用[9,10]。布地奈德混悬液为经典的糖皮质激素药物之一，能改善哮喘患儿肺功能和气道高反应性，调节Th1和Th2型细胞因子的平衡，并可调节神经内分泌免疫网络[11,12]。另外，布地奈德混悬液也具有抗炎、抗病毒、抗氧化、抗变态反应等多种药理作用[13,14]。本文具体探讨了布地奈德混悬液对哮喘幼鼠上皮-间充质转化和气道重塑的影响及机制，现总结报道如下。

1 材料与方法

1.1 研究材料

选择新生24 h之内C57BL6系SPF级幼鼠40只（共8只母鼠所生）购自北京维通利华公司（批号：201811422），饲养于本院实验动物中心，前4周以各自母鼠母乳喂养，4周后分笼饲养。饲养条件：恒定室温（20℃-25℃），光照12 h/d，湿度50%-60%。

吸入用布地奈德混悬液购自阿斯利康制药有限公司，抗E-cadherin抗体、抗NF-κB抗体购自北京中杉金桥生物技术有限公司，血清TNF-α、HO-1酶联免疫检测试剂盒购自武汉博士德生物工程有限公司，卵清蛋白购自国药集团。

1.2 哮喘幼鼠模型的建立

幼鼠分笼饲养1周后，在实验1d和3d采用50μl致敏液（0.1%卵清蛋白）行腹腔注射，因幼鼠腹壁较薄，腹腔注射时注意将幼鼠头部朝下放置，注射后注意按压针孔数分钟。然后在实验第15 d将将致敏幼鼠放于密闭容器（20 cm×20 cm×30 cm）内雾化吸入1.0%卵清蛋白20 min，1次/d，每次30 min，共4周。

幼鼠出现口唇发绀、腹肌痉挛、点头呼吸及站立不稳、呼吸加快表明建模成功。

1.3 幼鼠分组与处理

将建模成功的幼鼠（n=36）随机平分为三组-模型组、布地奈德1组、布地奈德2组，三组分别给予雾化吸入生理盐水、布地奈德混悬液0.1 mg与布地奈德混悬液0.2 mg，1次/d，共14 d。

1.4 观察指标

（1）观察与记录幼鼠的发育情况，即幼鼠的毛色、体重、活力状况。（2）在治疗第14 d 1%戊巴比妥钠腹腔注射麻醉幼鼠，然后眼球放血后进行处死。收集幼鼠的支气管肺泡灌洗液，测定白细胞总数与嗜酸性粒细胞总数。（3）取幼鼠的眼球血0.2 mL左右，4℃、1000 rpm离心10 min，取上清液，采用酶联免疫法检测血清肿瘤坏死因子（Tumor necrosis factor，TNF）-α、血红素加氧酶（heme oxygenase，HO）-1含量。（4）分离幼鼠的气道平滑肌，制成病理切片后，在镜下找到肺内支气管横断面，采用分析系统测定与计算支气管壁厚度（WAt/Pi）、支气管壁平滑肌细胞核数量（N/Pi）、支气管壁平滑肌厚度（WAm/Pi）等指标。（5）取幼鼠的肺组织标本，从肺组织中提取细胞总蛋白，定量蛋白含量有，SDS-PAGE电泳分离，转膜，将膜封闭后依次加入一抗（抗E-cadherin抗体、抗NF-κB抗体），辣根过氧化物酶标记的相应二抗，化学发光显示目的条带，测定与计算E-cadherin、NF-κB蛋白相对表达水平。

1.5 统计学方法

所有数据使用SPSS25.00软件完成统计学处理，统计结果用均数±标准差来表示，计量资料比较采用t检验，多组间差异比较采用单因素方差分析与one-way分析，$P<0.05$表示组间差异具有统计学意义，检验水准为$\alpha=0.05$。

2 结果

2.1 一般情况对比

模型组：幼鼠出现鼻煽、点头呼吸、偶尔咳嗽、呼吸加快加深、烦躁、前肢缩抬等表现，毛发不顺，食欲下降。布地奈德1组、布地奈德2组：大便、毛发自行恢复正常，精神状态有所恢复，食欲较模型组好。

2.2 支气管肺泡灌洗液白细胞总数与嗜酸性粒细胞总数对比

布地奈德1组、布地奈德2组的支气管肺泡灌洗液白细胞总数与嗜酸性粒细胞总数均低于模型组（$P<0.05$），布地奈德2组也显著低于布地奈德1组（$P<0.05$）。见表1。

表1 三组气管肺泡灌洗液白细胞总数与嗜酸性粒细胞总数对比（$\times10^4$/mL）

Table 1 Comparison of total number of leukocytes and eosinophils in three groups（$\times10^4$/mL）

Groups	(n)	Total white cell count	Total Eosinophil population
Budennide group 2	12	6.38±0.47*#	0.89±0.09*#
Budennide group 1	12	11.09±1.38*	2.78±0.33*
Model group	12	25.63±3.14	15.28±2.15
F		19.372	29.773
P		0.000	0.000

Note: compared with the model group, *$P<0.05$; compared with Budinnide Group 1, #$P<0.05$.

2.3 血清 TNF-α、HO-1 含量对比

布地奈德 1 组、布地奈德 2 组的血清 TNF-α、HO-1 含量均显著低于模型组(P<0.05)，布地奈德 2 组也显著低于布地奈德 1 组(P<0.05)。见表 2。

表 2 三组血清 TNF-α、HO-1 含量对比(pg/mL)

Table 2 Comparison of serum TNF-α, HO-1 content of three groups (pg/mL)

Groups	(n)	TNF-α	HO-1
Budennide group 2	12	75.22±9.32*#	60.22±8.24*#
Budennide group 1	12	82.10±13.29*	71.00±11.84*
Model group	12	118.02±10.52	168.347±15.99
F		12.888	18.653
P		0.000	0.000

Note: compared with the model group, *P <0.05; compared with Budinnide Group 1, #P <0.05.

2.4 气道重塑指标对比

布地奈德 1 组、布地奈德 2 组的 WAt/Pi、N/Pi、WAm/Pi 均显著高于模型组，布地奈德 2 组也显著高于布地奈德 1 组(P<0.05)。见表 3。

表 3 三组气道重塑指标对比对比

Table 3 Comparison of airway remodeling indexes in the three groups

Groups	(n)	WAt/Pi($\mu m^2/\mu m$)	N/Pi($n/\mu m$)	WAm/Pi($\mu m^2/\mu m$)
Budennide group 2	12	11.18±0.32*#	0.028±0.003*#	8.78±0.23*#
Budennide group 1	12	6.87±0.13*	0.015±0.002*	4.56±0.18*
Model group	12	5.11±0.28	0.010±0.001	2.77±0.77
F		12.091	24.284	36.444
P		0.000	0.000	0.000

Note: compared with the model group, *P <0.05; compared with Budinnide Group 1, #P <0.05.

2.5 E-cadherin、NF-κB 蛋白相对表达水平对比

布地奈德 1 组、布地奈德 2 组的肺组织 E-cadherin、NF-κB 蛋白相对表达水平均显著低于模型组(P<0.05)，布地奈德 2 组也显著低于布地奈德 1 组(P<0.05)。见表 4。

表 4 三组肺组织 E-cadherin、NF-κB 蛋白相对表达水平对比

Table 4 Comparison of relative expression of E-cadherin, NF-κB protein in three groups

Groups	(n)	E-cadherin	NF-κB
Budennide group 2	12	1.02±0.18*#	1.22±0.22*#
Budennide group 1	12	2.38±0.19#	2.55±0.28#
Model group	12	4.52±0.33	5.62±0.28
F		23.333	25.783
P		0.000	0.000

Note: compared with the model group, *P <0.05; compared with Budinnide Group 1, #P <0.05.

3 讨论

哮喘是世界范围内严重危害儿童健康的慢性呼吸系统疾病，随着病程的延长和气管炎症的进展，多数患儿会出现上皮 - 间充质转化和气道重塑现象，这也是哮喘不可逆性改变的重要原因之一[15]。哮喘的发生、发展过程非常复杂，成功的复制与人体相似的哮喘幼鼠模型，有助于进一步研究其发病机制[16,17]。卵蛋白具有很强的免疫原性，并且来源容易、价格低廉，是最常用哮喘模型的诱导物质，常采用雾化激发幼鼠，成功率高且致死率低[18]。本研究显示模型组幼鼠出现明显的活动过多、腹部凹陷、惊跳、搔耳挠鼻、前肢上抬行为，且其体重增长缓慢，表明哮喘幼鼠建模成功。

布地奈德是临床广泛应用的治疗哮喘的吸入型糖皮质激素，可减轻气管重塑，也可以抑制体外培养的支气管平滑肌细胞的增殖[19]。本研究显示布地奈德 1 组、布地奈德 2 组的支气管肺泡灌洗液白细胞总数与嗜酸性粒细胞总数都低于模型组(P<0.05)，布地奈德 2 组低于布地奈德 1 组(P<0.05)，结合 Méndez-Enríquez E 等[20]相关研究分析：哮喘状态持续可导致机体气道存在大量的嗜酸性粒细胞与淋巴细胞浸润，形成不可逆的气道阻塞。并且嗜酸性粒细胞可大量分泌白三烯、血小板活化因子等炎症因子，还可释放嗜酸性粒细胞等阳离子蛋白，可导致支气管平滑肌痉挛与增加气管微血管通透性，导致机体出现气道粘膜水肿，从而产生气道高反应性[21]。另外，Racanelli A C 等[22]研究显示：布地奈德能够降低白细胞总数与嗜酸性粒细

胞总数，从而可减轻气道炎症，对哮喘有一定治疗作用，且存在剂量依赖性，本研究结果与其存在相似之处。

哮喘是一种以患儿气道高反应性和气道阻塞为特点的慢性非特异性炎症，近端支气管内的气管平滑肌细胞增多是气管重塑的重要特征之一[23]。现代研究表明哮喘的免疫学发病机理为 Th1 细胞分化降低，导致 Th1/Th2 细胞功能失衡，而 Th2 细胞可促进 B 细胞产生大量免疫球蛋白，从而诱发机体出现变态反应和慢性气道炎症[24]。本研究显示布地奈德 1 组、布地奈德 2 组的血清 TNF-α、HO-1 含量低于模型组(P<0.05)，布地奈德 2 组低于布地奈德 1 组(P<0.05)；布地奈德 1 组、布地奈德 2 组 WAt/Pi、N/Pi、WAm/Pi 都高于模型组，布地奈德 2 组高于布地奈德 1 组(P<0.05)，表明布地奈德混悬液在哮喘幼鼠的应用能促进道重塑，抑制 TNF-α、HO-1 的释放，结合相关研究[25,26]分析：TNF-α、HO-1 是一种应激蛋白，当机体遭受到外界的氧化应激的时候，机体会自发地促进 TNF-α、HO-1 的释放，从而激活体内的抗氧化保护系统。另外，也有研究[27,28]显示：布地奈德能够减轻 Th1/Th2 细胞功能失衡的程度，并可与胞质中的糖皮质激素受体结合，可使机体的 T 淋巴细胞内游离钙增加，可以通过影响巨噬细胞来增强细胞的免疫作用，从而抑制 TNF-α、HO-1 的表达，从而为本研究结论做出解释。

哮喘是由多种细胞和细胞组分参与的气道慢性炎症疾病，这些慢性炎症同时导致了气道反应性的增加，导致哮喘的发作[29]。随着生活习惯、饮食结构及环境的变化，哮喘的患病率和死亡率都呈现上升趋势。布地奈德作为一个强效的糖皮质激素，能降低呼吸道高反应性，也能通过抑制趋化因子和内皮活化介质的产生或释放减轻气道炎症[30]。本研究显示布地奈德 1 组、布地奈德 2 组的肺组织 E-cadherin、NF-κB 蛋白相对表达水平低于模型组 (P<0.05)，布地奈德 2 组低于布地奈德 1 组 (P<0.05)，表明布地奈德混悬液在哮喘幼鼠的应用能抑制上皮 - 间充质转化。当前也有研究显示布地奈德能够抑制白介素 (Interleukin，IL)-1β 的产生，使促炎症因子蛋白质表达减少，从而发挥抗炎等生物学效应[31]。另外，布地奈德也可抑制变应原诱发的幼鼠嗜酸性粒细胞浸润，可以改善微循环，增强收缩心肌功能，抑制氧化应激作用，从而发挥其对抗上皮 - 间充质转化的作用，与本研究结果相符[32,33]。另外，本研究也存在一定的不足，没有设置其他药物治疗组，纳入幼鼠数量也比较少，将在后续研究中进行详细探讨。

总之，布地奈德混悬液在哮喘幼鼠的应用能抑制上皮 - 间充质转化和气道重塑，也可抑制 TNF-α、HO-1 的释放，减轻嗜酸性粒细胞与白细胞的浸润，从而发挥肺保护作用，且存在剂量依赖性。本研究对布地奈德在哮喘中的作用机制进行深入分析，从而为该疾病的临床治疗新思路的开发提供实验基础。

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