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论文

ESR和CLSM技术用于促渗剂作用机制及亲水性大分子跨鼻黏膜转运途径的研究

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摘要：

采用电子自旋共振(ESR)和共聚焦激光扫描显微镜(CLSM)技术研究促渗剂作用机制及促渗剂对亲水性大分子跨鼻黏膜转运途径的影响。比较重组水蛭素-2(rHV2)与促渗剂联合鼻腔用药前后大鼠的生物利用度；采用以5-噁唑烷氮氧自由基硬脂酸、16-噁唑烷氮氧自由基硬脂酸和马来酰亚胺作为自旋标记物的电子自旋共振技术，考察促渗剂对家兔鼻黏膜脂质和蛋白的影响；采用共聚焦显微镜光学切片结合荧光探针标记技术探讨促渗剂对大鼠鼻黏膜上皮细胞骨架肌动蛋白的作用，同时观察在各种促渗剂作用下rHV2的转运途径。壳聚糖(chitosan,CS),羟丙基-β-环糊精(hydroxyl-propyl-beta-cyclodextrin,HP-β-CD),甘草酸单胺盐(ammonium glycyrrhizinate,AMGZ)均能显著改善rHV2的鼻黏膜吸收；CS主要通过细胞旁路途径增加rHV2鼻黏膜转运，这一结果可能与其对细胞骨架肌动蛋白微丝的影响从而打开细胞间紧密连接有关；HP-β-CD可同时增加跨细胞和经细胞旁路两种途径的转运，可能与其既能改变膜质流动性又能影响膜蛋白构象的特性有关；AMGZ主要增加亲水性大分子跨细胞途径的转运，实验观察到其对膜蛋白有作用，但未观察到其对膜质的作用，确切的机制尚有待研究。本实验可为促渗剂及亲水大分子跨细胞膜转运途径的研究提供借鉴。

关键词： 促渗剂 亲水性大分子 电子自旋共振 共聚焦激光扫描显微镜 促渗机制 鼻黏膜 转运途径

Promoting mechanism of enhancers and transport pathway of large hydrophilic molecular across nasal epithelium studied by ESR and CLSM technologies

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Abstract:

The aim of this study is to investigate absorption-promoting mechanism of enhancers and the transport pathway of large hydrophilous molecular across rat nasal epithelium by electron spin resonance (ESR) and confocal laser scanning microscopy (CLSM) technologies. In the experiment, recombinant hirudin-2 (rHV2) was chosen as a large hydrophilic molecular model drug. After nasal administration in rats the bioavailability of rHV2 with or without various enhancers was compared. The effects of enhancers on membrane lipid fluidity and protein conformation were measured with 5-deoxyl-stearic acid (5-DSA), 16-deoxyl-stearic acid (16-DSA) and 3-maleidoproxyl (MSL) labeling ESR. The effects of enhancers on cytoskeletal F-actin of rat nasal epithelium and FITC-rHV2 transport pathway across rat nasal epithelium were performed by CLSM combined with fluorescence labeling. 0.5% Chitosan (CS), 5% hydroxyl-propyl-beta-cyclodextrin (HP-β-CD) and 1% ammonium glycyrrhizinate (AMGZ) were all able to significantly increase the nasal absorption of rHV2. CS could result in the paracellular pathway transport of FITC-rHV2 which seemed related to a transient effect on tight junctions. HP-β-CD could cause paracellular and transcellular route transport of FITC-rHV2 by influencing upon membrane protein as well as lipid fluidity. AMGZ seemed to enhance the transcellular route transport of FITC-rHV2, and could exert some influence on membrane protein but not on lipid fluidity. So how it brought out this result needs further research. Present experiment may become a useful reference for promoting mechanism of enhancers and the transport pathway of large hydrophilic molecular across nasal epithelium research.

Keywords: large hydrophilic molecular electron spin resonance confocal laser scanning microscopy absorption-promoting mechanism nasal epithelium transport pathway absorption enhancer

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