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论文

利用人源Caco-2细胞单层模型研究罂粟碱、*N*-甲基四氢罂粟碱和头花千金藤碱在人肠道的吸收

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摘要：

研究罂粟碱(papaverine，PAP)、*N*-甲基四氢罂粟碱(laudanosine，LAU)和头花千金藤碱(cepharanthine，CEP)在人小肠的吸收。利用人源结肠腺癌细胞系Caco-2细胞单层模型研究PAP、LAU和CEP由绒毛面(AP侧)到基底面(BL侧)、BL侧到AP侧两个方向的转运过程。应用HPLC-UV对上述3个生物碱进行定量分析，计算转运参数和表观渗透系数，并与易吸收性对照药普萘洛尔和难吸收性对照药阿替洛尔进行比较。PAP、LAU和CEP由AP侧到BL侧的表观渗透系数(P_{app})分别为$(3.524\pm0.223)\times10^{-5}$、$(2.821\pm0.050)\times10^{-5}$和$(6.524\pm0.052)\times10^{-5}$ cm·s^{-1}；由BL侧到AP侧的P_{app}分别为$(5.095\pm0.508)\times10^{-5}$、$(2.646\pm0.146)\times10^{-5}$和$(5.495\pm0.036)\times10^{-5}$ cm·s^{-1}，与在Caco-2细胞单层模型上呈良好吸收的阳性对照药普萘洛尔基本一致。PAP、LAU和CEP的$P_{app\ A\to B}/P_{app\ B\to A}$分别为0.69、1.07和1.19；PAP外流是摄取的1.45倍。PAP、LAU和CEP可以通过小肠上皮细胞被动吸收进入体内，属于良好吸收的药物。在三者的吸收转运过程中，油/水分配系数起着关键性的作用。PAP在Caco-2细胞单层模型中的转运可能存在外流机制。

关键词： Caco-2细胞单层 罂粟碱 *N*-甲基四氢罂粟碱 头花千金藤碱 肠吸收 表观渗透系数

Absorption of papaverine, laudanosine and cepharanthine across human intestine by using human Caco-2 cells monolayers model

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Abstract:

Absorption of papaverine (PAP), laudanosine (LAU) and cepharanthine (CEP) as some chemical constituents of traditional Chinese medicines in human intestine were studied. By using Caco-2 (the human colonic adenocarcinoma cell lines) cell monolayers as an intestinal epithelial cell model, the permeability of PAP, LAU and CEP were studied from apical side (AP side) to basolateral side (BL side) or from BL side to AP side. The three alkaloids were measured by reversed-phase high-performance liquid chromatography coupled with UV detector. Transport parameters and apparent permeability coefficients (P_{app}) were then calculated and compared with those of propranolol as a control substance of high permeability and atenolol as a control substance of poor permeability. The P_{app} values of PAP, LAU and CEP were $(3.524\pm0.223)\times10^{-5}$, $(2.821\pm0.050)\times10^{-5}$ and $(6.524\pm0.052)\times10^{-5}$ cm·s^{-1} from AP side to BL side, and $(5.095\pm0.508)\times10^{-5}$, $(2.646\pm0.146)\times10^{-5}$ and $(5.495\pm0.036)\times10^{-5}$ cm·s^{-1} from BL side to AP side, respectively. Their P_{app} values were identical with those of propranolol, which is a transcellular transport marker. On the other hand, the efflux transport of PAP was 1.45 times higher than its influx transport with 0.69 rate of $P_{app\ A\to B}/P_{app\ B\to A}$. But $P_{app\ A\to B}/P_{app\ B\to A}$ values of LAU and CEP were 1.07 and 1.19, respectively, which suggested that the efflux transport have not been involved in their absorbed mechanism in Caco-2 cells monolayers. There is a good correlation between the P_{app} value and apparent distribution coefficient (Log D) at pH 7.35 for the three alkaloids. PAP, LAU and CEP can be absorbed across intestinal epithelial cells, and they are completely absorbed compounds. PAP may have been involved in efflux mechanism in Caco-2 cells monolayers model from the basolateral-to-apical direction. The O/W (oil/water) partition coefficient plays key role in their transmembrane permeation.

Keywords: papaverine laudanosine cepharanthine intestinal absorption apparent permeability coefficient Caco-2 cell monolayer

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