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论著

# 邻苯二甲酸二乙基己基酯对新生大鼠肺组织发育的影响

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摘要 目的 探讨基质金属蛋白酶9(MMP-9)、金属蛋白酶1组织抑制剂(TIMP-1)和转化生长因子$\beta_1$(TGF-$\beta_1$)是否参与邻苯二甲酸二乙基己基酯(DEHP)影响肺组织形态发育的过程。方法 SD新生大鼠于出生后第1天开始分别ip给予DEHP 10, 100和750 mg·kg$^{-1}$, 每天1次。每组1/2大鼠持续染毒14 d, 剩余1/2大鼠持续染毒21 d。染毒结束后第2天处死大鼠, 取新鲜肺组织, 提取总RNA, 用实时定量PCR方法检测MMP-9, TIMP-1和TGF-$\beta_1$ mRNA 的表达;其余部分石蜡包埋, 制备石蜡切片, HE染色进行组织形态观察, 或者免疫组化染色检测MMP-9, TIMP-1和TGF-$\beta_1$蛋白表达。结果 DEHP染毒14 d, 与溶剂对照组比较, DEHP 100和750 mg·kg$^{-1}$组新生大鼠肺泡发育受抑制, 肺间质比例增大($P$<0.05);DEHP 10, 100和750 mg·kg$^{-1}$组MMP-9和TGF-$\beta_1$ mRNA表达随着DEHP染毒剂量的增加而增加($r$= 0.979, $P$<0.01; $r$=0.990, $P$<0.01), MMP-9和TGF-$\beta_1$蛋白表达亦随着DEHP染毒剂量的增加而增加($r$=0.770, $P$<0.01; $r$=0.959, $P$<0.01);TIMP-1 mRNA和蛋白表达下降($r$=0.904, $P$<0.01; $r$=0.795, $P$<0.01)。DEHP染毒21 d, DEHP 10, 100和750 mg·kg$^{-1}$组肺间质比例与溶剂对照组比较无明显变化; MMP-9和TGF-$\beta_1$ mRNA表达随着DEHP染毒剂量的增加而下降($r$=0.879, $P$<0.01; $r$=0.904, $P$<0.01), MMP-9和TGF-$\beta_1$蛋白表达亦随着DEHP染毒剂量的增加而下降($r$=0.935, $P$<0.01; $r$=0.819, $P$<0.01);TIMP-1 mRNA和蛋白表达增加($r$=0.819, $P$<0.01; $r$=0.619, $P$<0.01)。结论DEHP通过影响肺组织MMP-9, TIMP-1和TGF-$\beta_1$基因和蛋白的表达影响新生大鼠肺组织形态发育。

关键词 邻苯二甲酸二乙基己基酯 肺 基质金属蛋白酶9 金属蛋白酶1组织抑制剂 转化生长因子$\beta_1$

分类号 R992

# Effect of di-(2-ethylhexyl)phthalate exposure on lung tissue development in newborn rats

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**Abstract**

**OBJECTIVE** To investigate the role of matrix metalloproteinase 9 ( MMP-9 ), tissue inhibitor of metalloproteinase-1 (TIMP-1 ), and transforming growth factor-$\beta_1$ ( TGF-$\beta_1$) in the toxic effect of di-(2-ethylhexyl)phthalate(DEHP) on lung development. **METHODS** The newborn Sprague-Dawley rats were ip given DEHP 10, 100 and 750 mg·kg$^{-1}$ daily, half from the postnatal 1st day to the postnatal 14th day, and the other half from the postnatal 1st day to the postnatal 21st day. All of the rats were sacrificed on the next day after the last DEHP administration. The fresh lung tissue was taken for RNA extraction. The MMP-9, TIMP-1, and TGF-$\beta_1$ mRNA expression in lung tissue was measured by real time PCR. The lung tissue morphological changes were observed by HE staining. The protein expression of MMP-9, TIMP-1 and TGF-$\beta_1$ in lung tissue was also examined by immunohistochemistry. **RESULTS** On the postnatal 14th day, the alveolar growth inhibition and thicker alveolar septa were detected during the morphological examination of DEHP 100 and 750 mg·kg$^{-1}$ groups compared with the solvent control group($P$<0.05). The mRNA expression of MMP-9 and TGF-$\beta_1$ in DEHP 10, 100 and 750 mg·kg$^{-1}$ groups was increased dosage dependently($r$=0.979, $P$<0.01; $r$=0.990, $P$<0.01), so did the protein expression of MMP-9 and TGF-$\beta_1$ of DEHP 10, 100 and 750 mg·kg$^{-1}$ groups($r$=0.770, $P$<0.01; $r$=0.959, $P$<0.01). Meanwhile, the expression of TIMP-1 mRNA and protein was decreased($r$=0.770, $P$<0.01; $r$=0.959, $P$<0.01). On

the postnatal 21st day, there was no significant change in the ratio of lung interstitial tissue between the solvent control and DEHP groups. The mRNA expression of MMP-9 and TGF-$\beta_1$ in DEHP 10, 100 and 750 mg • $kg^{-1}$ groups was decreased with the increase in DEHP dose($r$=0.879, $P$<0.01; $r$=0.904, $P$<0.01), like the protein expression($r$=0.935, $P$<0.01; $r$=0.819, $P$<0.01), while the expression of TIMP-1 mRNA and protein was increased($r$=0.819, $P$<0.01; $r$=0.619, $P$<0.01).
**CONCLUSION** DEHP inhibits the alveoli morphological development of newborn rats by interfering the gene and protein expression of MMP-9, TIMP-1 and TGF-$\beta_1$.

**Key words** diethylhexylphthalate lung matrix metalloproteinase 9 tissue inhibitor of metalloproteinase-1 transforming growth factor $\beta_1$

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