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论著

氟哌啶醇对人红白血病耐多柔比星细胞株多药耐药性的逆转及其机制

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摘要 目的 从临床常用药物中探寻逆转肿瘤耐药性的活性物质。方法 应用MTT法测定不同浓度Hal处理的瘤细胞对0～20 μmol·L^{-1}多柔比星(Dox)的敏感性的影响。RT-PCR法分析12.5 μmol·L^{-1}氟哌啶醇(Hal)处理后多药耐药基因(MDR1), 多药耐药相关蛋白(MRP)和谷胱甘肽*S*转移酶Pi(GSTπ)mRNA表达的变化。通过流式细胞术观察0, 6.25, 12.5, 25 μmol·L^{-1} Hal对细胞内药物蓄积和细胞周期进程的影响。结果 Hal对K562/Dox的耐药性具有明显的逆转作用。在12.5, 6.25及3.125 μmol·L^{-1}时的逆转倍数分别为8.35, 4.21及2.16。用12.5 μmol·L^{-1} Hal处理后，MDR1及MRP的mRNA表达水平均呈现时间依赖性明显降低，分别较原水平下降76.3%及64.6%。药后d 2 GSTπ mRNA表达下降66.1%, 于d 3回升。Hal处理细胞1 h后, Dox在细胞内蓄积量明显增加, 并呈浓度依赖性；此外, Hal可明显增强Dox对K562/Dox细胞的G_2/M阻滞作用，12.5 μmol·L^{-1}浓度可以使5 μmol·L^{-1} Dox的G_2/M阻断由单独应用时的9.9%±4.3%增加到23.4%±3.0%。结论 Hal具有较强的逆转K562/Dox细胞MDR的作用，其逆转机制为多种途径，包括相关基因mRNA的表达下调，增加细胞内药物蓄积，增强Dox对K562/Dox在G_2/M期的阻滞作用。

关键词 氟哌啶醇 多柔比星 多药耐药 细胞系, K562 细胞系, MCF-7

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Reversal effect of haloperidol on multidrug resistance of doxorubicin-resistant erythroleukemic cell line and its mechanism

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Abstract

AIM To explore the activity to reverse the multidrug resistance(MDR) of cancer chemotherapy in clinical drugs. **METHODS** Using tetrazolium dye assay(MTT), the effects of various concentrations of haloperidol(Hal) on cytotoxicity in K562/Dox cells at 0－20 μmol·L^{-1} doxorubicin(Dox) were studied. Expression of MDR related genes MDR1, glutathoine *S*- transferase Pi(GSTπ) and MDR associated protein(MRP) of K562 /Dox treated with 12.5 μmol·L^{-1} Hal were assayed by reverse transcription polymerase chain reaction(RT-PCR). Using flow cytometry(FCM), intracellular Dox accumulation in K562/Dox cells treated by 0, 6.25, 12.5 and 25 μmol·L^{-1} Hal and its effects on cell cycle progression were observed. **RESULTS** Hal significantly reversed MDR in K562/Dox cells after 12.5, 6.25 and 3.125 μmol·L^{-1} Hal treatment, the chemosensitivity to Dox increased by 8.35, 4.21 and 2.16 times respectively. After treatment with Hal 12.5 μmol·L^{-1}, MDR1 and MRP mRNA gene expression were gradually downregulated in a time-dependent manner in d 1－3. On the third day MDR1 and MRP reached the lowest level (76.3% and 64.6% of the control level, $P<0.05$) while GSTπ mRNA level decreased by 66.1% ($P<0.05$) in the first two days, and began to recover on d 3. One hour after Hal 25, 12.5 and 6.25 μmol·L^{-1} treatment, intracellular Dox accumulation increased in a concentration dependent manner. FCM data showed that after 48 h treatment with combination of Hal and Dox, a significant G_2/M phase block in the cell cycle occurred in K562/Dox cells with the increase in Hal concentrations. The G_2/M block by 5 μmol·L^{-1} Dox alone or in combination with 12.5 μmol·L^{-1} Hal were 9.9%±4.3% and 23.4%±3.0%, respectively. **CONCLUSION** A nontoxic concentration of Hal appeared to potentiate the cytotoxicity of Dox through a multi-pathway, including down regulating mRNA of MDRI, GSTπ and MRP, increasing intracellular drug concentration and enhancing the G_2/M arrest of Dox in the cell cycle.

Key words

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