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哇巴因抑制结直肠癌多药耐药细胞增殖及侵袭力的研究

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Mechanism of Inhibitory Effect of Ouabain on the Proliferation and Invasion of Human Colorectal Cancer Multidrug-Resistant Cells

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摘要

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摘要 探讨结直肠癌耐药细胞增殖及侵袭力与Na+，K+-ATP酶活性及其β1亚单位和P糖蛋白（P-gp）表达的关系，及哇巴因增加化疗敏感性的可能机制。方法：以人结直肠癌亲本细胞（SW480）和耐奥沙利铂细胞（SW480/OxR）为研究对象，采用MTS法、Transwell小室、生化酶学、实时定量PCR（Real time quantitative，RT-PCR）及流式细胞技术等方法比较SW480细胞与SW480/OxR细胞的增殖及侵袭力、Na+，K+-ATP酶活性及其β1亚单位和P-gp表达的差异，观察哇巴因对SW480/OxR细胞上述指标的影响。结果：与SW480细胞比较，SW480/OxR细胞增殖活力无明显变化（P>0.05），而细胞侵袭力却显著增加，Na+，K+-ATP酶活性下降，β1亚单位表达下调，P-gp表达上调（P均<0.01）；哇巴因能显著抑制SW480/OxR细胞增殖活力，减弱其侵袭力，下调SW480/OxR细胞P-gp蛋白表达，上调SW480/OxR细胞β1亚单位蛋白表达，增加SW480/OxR细胞Na+，K+-ATP酶活性（P均<0.01）。结论：Na+，K+-ATP酶活性下降可能源于β1亚单位表达下调，并参与结直肠癌的耐药；哇巴因能部分逆转结直肠癌耐药细胞MDR，可能与增加Na+，K+-ATP酶活性及下调P-gp表达有关。

关键词： 结直肠癌 腺苷三磷酸酶 P-糖蛋白 化疗抵抗 哇巴因

Abstract: This work aimed to explore the effects of Na+/K+-ATPase activity and the expression of its β1-subunit and P-glycoprotein (P-gp) on the proliferation and invasion of human colorectal cancer parental cells (SW480) and oxaliplatin-resistant cells (SW480/OxR). The molecular mechanisms of ouabain for reversing the multidrug resistance (MDR) of human colorectal cancer oxaliplatin-resistant cells were also examined. Methods: SW480 and SW480/OxR cells derived from the same patient were treated with or without ouabain at the physiological concentration of 1 nM. The SW480 and SW480/OxR cell proliferation capacity was assessed by the MTS assay. The invasion capacity was deteremined using a Transwell chamber. The Na+/K+-ATPase activity was measured by biochemical and enzymological techniques. The expression of the β1-subunit and P-gp of Na+/K+-ATPase was determined by real-time quantitative PCR, Western blotting, and flow cytometry. Results: The capacity of invasion significantly increased in the SW480/OxR cells compared with the SW480 cells (P < 0.01). There was no difference between the SW480 and SW480/OxR cell proliferation capacities (P > 0.05). The Na+/K+-ATPase activity significantly decreased in SW480/OxR cells compared with SW480 cells (P < 0.01). The expression of the Na+/K+-ATPase β1-subunit in mRNA and protein levels was lower in SW480/OxR cells than in SW480 cells (P < 0.01). However, the expression of P-gp in mRNA and protein levels was higher in SW480/OxR cells than in SW480 cells (P < 0.01). Interestingly, ouabain at the physiological concentration of 1 nM significantly enhanced the activity of Na+/K+-ATPase in SW480/OxR cells (P < 0.05). The expression of the β1-subunit was also upregulated and that of P-gp was downregulated at the protein level, thereby inducing a decrease in the capacity of SW480/OxR cell growth inhibition and invasion. Nevertheless, after ouabain treatment for 48 h, the Na+/K+-ATPase activity and β1-subunit protein expression level in SW480/OxR cells were still lower than those in SW480 cells (P < 0.01). Conclusion: Decreased Na+/K+-ATPase activity can be attributed to the downregulation of Na+/K+-ATPase β1-subunit expression and may cause the MDR of human colorectal cancer cells. Ouabain could partly reverse the MDR of such cells, which can be

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attributed to increased Na+/K+-ATPase activity and P-gp expression downregulation.

Key words: Colorectal cancer Na+/K+-ATPase P-glycoprotein Multidrug resistance of chemotherapy Ouabain

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