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论著

N-乙酰半胱氨酸对化疗所致骨髓抑制的改善作用

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摘要 目的 探讨N-乙酰半胱氨酸(NAC)对化疗所致骨髓抑制的改善作用。方法 1 体内实验:将C57BL/6j小鼠随机分为正常对照组、环磷酰胺(Cy)所致骨髓抑制模型对照组(ip给予生理盐水)以及模型＋NAC 30,90和270 mg·kg^{-1}组,每天1次,连续10 d。给药第4天一次性ip给予Cy 380 mg·kg^{-1}制备骨髓抑制小鼠模型。造模后第1,2,3,4和7天,鼠尾静脉取血20 μl检测外周血像,同时取一侧股骨骨髓,检测骨髓单个核细胞(BM-MNC)数目;造模后第1天,检测BM-MNC凋亡和细胞内活性氧(ROS)水平。2 体外实验:C57BL/6j小鼠一次性ip给予Cy 380 mg·kg^{-1}后第3天,取BM-MNC进行造血祖细胞培养,在培养体系中加入NAC 0.01, 0.1, 1和5 mmol·L^{-1},于第7~12天检测造血祖细胞粒红巨噬巨核系集落形成单位(CFU-Mix)、粒细胞巨噬细胞集落形成单位(CFU-GM)和红系爆式形成单位(BFU-E)数目,观察NAC体外对骨髓抑制模型小鼠造血祖细胞增殖分化的影响。结果 1 体内实验:与正常对照组相比,ip给予Cy后第1~4天,模型组BM-MNC和外周血白细胞(WBC)数目显著下降,造模后第7天仍未恢复正常。与模型组相比,造模第2天,NAC 270 mg·kg^{-1}组WBC数目降低;其余各时间点,NAC各治疗组的WBC数目无明显差异,NAC 30和90 mg·kg^{-1}组WBC最低值于造模后第4天出现。与模型组比较,造模后第1天NAC 30和90 mg·kg^{-1}组ROS水平降低,BM-MNC凋亡率无明显差异; 造模后第1~2天BM-MNC明显增加。2 体外实验:与正常对照组相比,模型组造血祖细胞CFU-Mix,CFU-GM和BFU-E数目均明显降低;与模型组比较,NAC 0.1 mmol·L^{-1}能够增加骨髓抑制小鼠骨髓造血祖细胞CFU-GM和BFU-E数目,但NAC 5 mmol·L^{-1}减少模型小鼠CFU-GM,BFU-E和CFU-Mix数目。结论 NAC通过降低ROS水平对化疗所致骨髓抑制有一定的改善作用。

关键词 N-乙酰半胱氨酸 骨髓细胞 药物疗法 造血干细胞

分类号 R965

Effect of N-acetylcysteine on myelosuppression induced by chemotherapy

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Abstract

OBJECTIVE To explore the effect of N-acetylcysteine (NAC) on myelosuppression induced by chemotherapy in mice. **METHODS** *In vivo* experiments, C57BL/6j mice were randomly divided into normal and myelosuppression groups. Myelosuppression mice were ip given once daily NAC 30, 90 and 270 mg • kg^{-1}or normal saline, respectively, for 10 consecutive days and were treated (ip) with cyclophosphamide (Cy) on the 4th day to induce myelosuppression. Blood 20 μl from mouse tail was collected to measure peripheral hemogram, and bone marrow in a femur was collected to measure the number of bone marrow mononuclear cells (BM-MNC) on the 1st, 2nd, 3rd, 4th and 7th days after Cy treatment. Apoptosis and the reactive oxygen species (ROS) level of BM-MNC were measured on the 1st day after Cy treatment. *In vitro* experiment, the mice were once ip given Cy 380 mg • kg^{-1} and on the 3rd day the hemotopietic progenitor cells (HPC) were prepared. NAC 0.01, 0.1, 1 and 5 mmol • L^{-1} were added into the culture system of HPC to measure the number of colony forming unit-granulocyte, erythrocyte, macrophage and megakaryocyte (CFU-Mix), colony forming unit-granulocyte-macrophage (CFU-GM) and burst forming unit-erythroid (BFU-E). The effect of NAC on proliferation and differentiation of HPC in myelosupressed mice was studied. **RESULTS** *In vivo* experiments, the number of BM-MNC and white blood cells (WBC) decreased markedly from the 1st day to the 4th day after Cy treatment and the numbers were still not back to normal on the 7th day after Cy treatment. Compared with normal control, NAC 270 mg • kg^{-1} reduced the number of WBC in peripheral blood on the 2nd day after Cy treatment, and there was no significant difference between the NAC treatment groups at other examination time points, but the time of the lowest WBC count in NAC 30 and 90 mg • kg^{-1} groups was postponed. Compared with model group, NAC 30 and 90 mg • kg^{-1} reduced the level of ROS, but increased the count of BM-MNC significantly on the 1st day and on the 2nd day after Cy treatment. NAC had no marked effects on apoptosis of BM-MNC between NAC treatment groups and model group. *In vitro* experiment, compared with normal group, the number of CFU-GM, BFU-E and CFU-Mix in myelosuppression model group significantly reduced. Compared with the model group, NAC 0.1 mmol • L^{-1} increased the numbers of CFU-GM and BFU-E, but NAC 5 mmol • L^{-1}

decreased the number of CFU-GM, BFU-E and CFU-Mix. **CONCLUSION** NAC improves myelosuppression by reducing ROS level of BM-MNC in myelosuppressed mice.

Key words N-acetylcysteine bone marrow cells drug therapy hematopoietic stem cells

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