Nitric oxide and BCNU chemoresistance in C6 glioma cells: role of S-nitrosoglutathione.

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Abstract

Inducible nitric oxide synthase (iNOS or NOS2) is expressed in malignant glioma. Previously we noted that C6 glioma cells overexpressing NOS2 displayed chemoresistance against 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and other chloroethylnitrosourea derivatives with carbamoylating action. Herein we report experimental evidence supporting the contention that this NOS2 effect is mediated, at least in part, by S-nitrosoglutathione (GSNO), a potent antioxidant derived from interaction of NO and glutathione. Out of three NO donors tested, only GSNO was effective in protecting glioma cells against BCNU cytotoxicity. Furthermore, the protective effect of GSNO, similar to that of NOS2, was confined to carbamoylating, but not alkylating action. Experimental manipulations that were expected to increase or decrease cellular GSNO stores, as confirmed by immunocytochemical staining using a GSNO-specific antibody and HPLC analysis of GSNO contents in culture medium, led respectively to enhanced or reduced chemoresistance against carbamoylating cytotoxicity. Finally, neocuproine, a selective cuprous ion chelator known to neutralize GSNO actions, abolished NOS2-mediated chemoresistance against carbamoylating agents. Our results reveal a novel action of NOS2/GSNO that may potentially contribute to the development of chemoresistance against BCNU, which remains a mainstay in chemotherapy for glioblastoma multiforme.