Pharmacological Reports
2008, 60, 171–182
ISSN 1734-1140

Proline-linked nitrosoureas as prolidase-convertible prodrugs in human breast cancer cells

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Abstract:
A number of novel proline-linked nitrosoureas (**1**–**4**) were synthesized and examined for cytotoxicity and influence on DNA and collagen biosynthesis in MDA-MB-231 and MCF-7 human breast cancer cells. Evaluation of the cytotoxicity of these compounds employing a MTT assay and inhibition of [^{3}H]thymidine incorporation into DNA in both MDA-MB-231 and MCF-7 breast cancer cells demonstrated that compound **2**, the most active of the series, proved to be only slightly less potent than carmustine. It has also been found that carmustine did not inhibit MCF-7 cells prolidase activity, while compounds **1**–**4** significantly increased its activity, when used at 50–250 μM concentrations. Proline-linked nitrosoureas (**1**–**4**) also had lower ability to inhibit collagen biosynthesis in MCF-7 cells, compared to carmustine. The expression of β_1-integrin receptor and phosphorylated MAPK, ERK_1 and ERK_2 was significantly decreased in MCF-7 cells incubated for 24 h with 60 μM of compounds **2** and **4** compared to the control, untreated cells, whereas under the same conditions carmustine did not evoke any changes in expression of all these signaling proteins, as shown by Western immunoblot analysis. These results indicate the proline-linked nitrosoureas (**1**–**4**), represent multifunctional inhibitors of breast cancer cell growth and metabolism.

Key words:
nitrosoureas, breast cancer cells, prolidase, collagen biosynthesis, β_1-integrin