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## Inhibitors of protein tyrosine phosphorylation reduce the proliferation of two human glioma cell lines.

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### Abstract

Epidermal growth factor (EGF) and platelet-derived growth (PDGF) are suggested to be involved in the proliferation of human gliomas. We examined the effects of these growth factors on two human malignant glioma cell lines. Treatment of the A172 glioblastoma and the Hs683 glioma cell line with EGF and PDGF resulted in the tyrosine autophosphorylation, and hence activation, of the respective growth factor receptors. In addition, both cell lines responded to EGF and PDGF with increased deoxyribonucleic acid (DNA) synthesis. Because the intrinsic protein tyrosine kinase activity of this class of growth factor receptors is indispensable for their functioning, we tested the effects of specific protein tyrosine kinase inhibitors on growth factor-induced DNA synthesis and glioma cell proliferation. Genistein inhibited both EGF- and PDGF-stimulated autophosphorylation of the receptors and induction of DNA synthesis. However, genistein seemed to be cytotoxic to the cells. The tyrphostins RG 50875 and RG 13022 dose-dependently inhibited DNA synthesis induced by EGF, PDGF, and serum. RG 13022 completely blocked the EGF- and PDGF-induced DNA synthesis at a concentration of 50  $\mu\text{mol/L}$ . The tyrphostins showed no selectivity in blocking either EGF or PDGF signaling. With concentrations up to  $\mu\text{mol/L}$ , no cytotoxic side effects of the tyrphostins were observed. Both tyrphostins also inhibit serum-driven cell growth in a dose-dependent manner. These results support the hypothesis that activated protein tyrosine kinase receptors are involved in the proliferation of A172 and Hs683 glioma cells. Selective inhibitors of protein tyrosine kinases, therefore, might have the potential to contribute to the treatment of growth factor-dependent gliomas.

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