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## Signal transduction for proliferation of glioma cells in vitro occurs predominantly through a protein kinase C-mediated pathway.

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### Abstract

Previous work has demonstrated that **glioma** cells have very high protein kinase C (PKC) enzyme activity when compared to non-malignant glia, and that their PKC activity correlates with their proliferation rate. The purpose of this study was to determine whether the elevated PKC activity in **glioma** is secondary to an autonomously active PKC isoform implying oncogenic transformation, or whether this activity is driven by upstream ligand-receptor tyrosine kinase interactions. We treated established human **glioma** cell lines A172, U563 or U251 with either the highly selective PKC inhibitor CGP 41 251, or with **genistein**, a tyrosine kinase inhibitor. The proliferation rate and PKC activity of all the **glioma** lines was reduced by CGP 41 251; the IC50 values for inhibiting cell proliferation corresponded to the IC50 values for inhibition of PKC activity. **Genistein** also inhibited cell proliferation, with IC50 proliferation values approximating those for inhibition of tyrosine kinase activity in cell free protein extracts. Importantly, in **genistein**-treated cells, downstream PKC enzyme activity was dose dependently reduced such that the correlation coefficient for effects of **genistein** on proliferation rate and PKC activity was 0.92. These findings suggest that upstream tyrosine kinase linked events, rather than an autonomously functioning PKC, result in the high PKC activity observed in **glioma**. Finally, fetal calf serum (FCS) evoked a strong mitogenic effect on **glioma** cell lines. This mitogenic activity was completely blocked by CGP 41 251, suggesting that although the many mitogens in FCS for **glioma** cells signal initially through **genistein**-inhibitable tyrosine kinases, they ultimately channel through a PKC-dependent pathway. We conclude that proliferative signal transduction in **glioma** cells occurs through a predominantly PKC-dependent pathway and that selectively targeting this enzyme provides an approach to **glioma** therapy.

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