

LONG-TERM EFFECTS OF GROWTH FACTORS ON NEUROGLIA: PROLIFERATION, DE-DIFFERENTIATION, AND NEUROGENESIS

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Subventricular zone astrocytes and ependymal cells have been implicated in neurogenesis in a few regions of the adult brain. Studies from our and other laboratories have shown that growth factors may induce de-differentiation of neuroglial cells and then promote their transformation into neuroblasts both in vivo and in vitro. Our experiments utilize C6-2B rat glioma, a mixed culture of astrocytes and oligodendrocytes. We added Epidermal Growth Factor (EGF) or Fibroblast Growth Factor (FGF) to the cultures in various doses and for various periods of time. Under these conditions, both growth factors increased cell proliferation (measured by cell count), but decreased specific enzymatic activity (measured by activity of the enzymes glutamine synthetase, GS, for astrocytes, and 2'3'-cyclic nucleotide 3'phosphohydrolase, CNP, for oligodendrocytes). Our past research found that during a 6-day period, the smallest effective doses for EGF and FGF were 50 ng/mL and 80 ng/mL, respectively. Using these concentrations, we are currently investigating whether EGF- and FGF- stimulated cell proliferation may be extended and enhanced over a 20-day period. The experimental data show that a longer period of exposure to the growth factors provides a more sustained proliferation. We have interpreted the association of greater proliferation with reduced enzymatic activity as a condition of de-differentiation. This conclusion is also supported by immunofluorescent imaging studies of the cells. Thus, it appears possible to maintain cultured neuroglia cells in an immature state by the administration of growth factors. Several observations from others have recently reported that progenitor neuroglia may generate neurons in the human brain. We are now testing by immunofluorescent imaging whether immature neuroglia can be induced to transform into neuroblasts and, eventually, neurons. *Supported by NIH AG 19145-03 and BioTime, Inc.*