

# Effects of Nutrient Availability and Alcohol Exposure on the Fate of Neural Stem Cells

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Chronic alcohol exposure is toxic to many types of cells and results in tissue, and eventually, organ damage. The detrimental effects of alcohol to the developing nervous system are seen in infants with Fetal Alcohol Syndrome. However, the mechanism(s) and pathways of neural damage remain unresolved. Using the mouse neural stem cell line C17.2 as a model, previous work in our laboratories has demonstrated that both glucose and lipids affect Fas (CD95) cell surface expression. Fas is a key immunomodulatory molecule that upon engagement directly impacts a cell's fate by either inducing a death signal or a proliferation signal. When C17.2 cells were incubated in medium containing increasing concentrations of glucose, the number of cells increased (likely as a result of an increased rate of cellular proliferation), while cell surface Fas decreased in a dose dependent manner. C17.2 cells adapted to low lipid conditions demonstrate a significantly higher level of cell surface Fas when compared to cells cultured in standard medium, but exhibit a significantly decreased growth rate. To determine if our data were the result of Fas signaling, the Fas receptor was engaged with anti-Fas antibodies. Fas receptor engagement had no observable effects on the growth of C17.2 cells cultured in normal medium, but the anti-Fas treatment of C17.2 cells maintained in medium with no glucose caused marked (61%) cell death. Replacing nutrient prevented Fas-induced death. Under low lipid conditions, engagement of Fas caused a slight, but reproducible *decrease* in the percent of cell death. These data suggest that the proliferation and cell death in neural stem cells are, at least in part, mitigated in a nutrient and Fas-dependent manner. Thus, we questioned whether ethanol (ETOH) might also exert its effects through Fas signals. When C17.2 cells were incubated with increasing concentrations of ETOH, Fas cell surface expression in C17.2 cells under normal nutritional conditions increased in a dose dependent manner, and the percent cell death showed a corresponding, albeit slight, increase. Conversely, ETOH induced a dose dependent decrease in cell surface Fas in C17.2 cells under low lipid conditions with no significant change in cell death until the highest concentrations of ETOH (0.5M) were reached. ETOH treatment resulted in a dose dependent decrease in cell surface Fas Ligand under both normal and low lipid conditions. Given that cell surface Fas Ligand is required for Fas-mediated cell death, this result may explain why C17.2 cells showed a negligible increase in cell death (low levels of both the receptor and ligand) unless the cells were cultured in exceedingly high concentrations of ETOH. Collectively, these results have important implications relative to the mechanism of ETOH-induced neural stem cell fate and may suggest that neural stem cells per se are spared ethanol induced damage and may suggest that neural stem cells might be triggered to replace damaged neurons in this disease.