BMC Pharmacology

Oral presentation

Role of nitric oxide and cyclic GMP in proliferation and differentiation of murine and human embryonic stem cells

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from 2nd International Conference of cGMP Generators, Effectors and Therapeutic Implications
Potsdam, Germany, 10–12 June, 2005

Published: 16 June 2005

BMC Pharmacology 2005, **5**(Suppl 1):S38 doi:10.1186/1471-2210-5-S1-S38

We hypothesized that the fundamental role of nitric oxide and cyclic GMP in numerous physiological processes would suggest that these mediators also participate in stem cell proliferation and differentiation. Mouse and human (H9) embryonic stem cells were cultured under standard conditions for various periods (one to 15 days). The hanging drop method was utilized to induce differentiation of stem cells into various cellular lineages including myocardial, neuronal precursor, neuronal, astrocyte and oligodendrocytes.

As determined by QT-PCR and Western immunoblots NOS-1 was elevated at day 1 and diminished over 7 to 12 days of culture. In contrast, NOS-2, NOS-3, and α and β subunits of soluble guanylyl cyclase and PKG were low at day one and progressively increased with proliferation and differentiation. The localization of these proteins could be found in myocardial cells, neural precursor cells, neural cells and glial cells with immunofluorescence (histochemistry and FACS) using colocalization with cell specific markers.

Under some conditions addition of ODQ, the soluble guanylyl cyclase inhibitor, increased the differentiation of stem cells into myocardial cells and decreased the differentiation into neural and glial cells. Addition of cyclic GMP analogues could overcome the ODQ effect with myocardial differentiation.

These studies support our hypothesis that NO and cyclic GMP influence stem cell proliferation and differentiation.

Other studies with pharmacologic and/or genetic manipulation of these stem cells are in progress.