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FGF2 and ET1 promote human fetal striatal neuroblasts survival in hypoxic conditions

Stefano Ambrosini[1], Annamaria Morelli[1], Erica Sarchielli[1], Pasquale Gallina[2] and Gabriella Barbara Vannelli[1]

[1] Department of Experimental and Clinical Medicine. Anatomy and Histology Section, University of Florence, 50134-Florence, Italy
[2] Department of Surgery and Translational Medicine, Neurosurgery Section, University of Florence, 50134-Florence, Italy

Fetal striatal transplantation emerged as a new strategy to promote reparative responses in Huntington's disease (HD) patients[1]. Mechanisms that support neuroblasts survival and replenishment of damaged cells within the HD brain in hypoxia remain to be elucidated. This study investigated how human fetal striatal neuroblasts (HSP cells) respond to hypoxia, using the hypoxia-mimetic agent cobalt chloride ($CoCl_2$)[2]. We analyzed $CoCl_2$ effect on hypoxia-related proteins, such as HIF-1α and VEGF, and on a neuroprotective factor, such as Seladin-1. Moreover, we evaluated FGF2 (50 ng/ml) and ET1 (100 nM) proliferative/survival effects in HSP cells in normoxic and hypoxic conditions. These growth factors could be important mediators under pathological conditions for striatal neuroblasts function and response to hypoxia. Dose-response experiments with increasing concentration of $CoCl_2$ (50-750 um) showed an increase of HSP cell proliferation at 24-48h, with maximal effects observed at 400 um, while cell survival was impaired at 72h. Hypoxia increased protein expressions of HIF-1α and VEGF, whereas decreased Seladin-1 levels. FGF2 and ET1 significantly stimulated HSP cells proliferation both in normoxic and hypoxic condition, counteracting the apoptotic $CoCl_2$ effect at 72h. FGF2 and ET1 neuroprotective effect was abolished by the selective inhibition of their receptors (FGFR1, ETA and ETB). In particular, ET1 stimulated HSP cells survival through ETA receptor in normoxic condition and through ETB receptor during hypoxia. Our results support the idea that FGF2 and ET1 promote neurogenesis and survival of HSP cells, through receptor-mediated mechanisms, when grafted into the hypoxic HD brain.

References

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Key words
Hypoxia, Human striatal neuroblasts, FGF-2, ET-1, Huntington's disease.