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Microglial downregulation in a double transgenic mouse model associated with early-onset Alzheimer's disease (AD) after intraventricular implantation of alginate encapsulated Glukagon-like-peptide-1 (GLP-1) producing human mesenchymal stem-cells

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Background

GLP-1 peptide is an endogenous insulinotropic peptide. GLP-1 receptors are expressed throughout the brains of rodents and humans. Intracerebroventricular GLP-1 administration reduced the levels of amyloid-beta peptide (Aβ) in diabetic mice and protected cultured hippocampal neurons against Aβ and iron induced stress suggesting that GLP-1 can modify amyloid precursor protein (APP) processing and protect against oxidative injury [1]. In the double transgenic mice model associated with early-onset AD, the effect of GLP-1 secreting human mesenchymal stem cells (hMSC) on A-β40/42 load, Aβ associated gliosis and microglial response were investigated in the present study.

Materials and methods

Alginate microcapsules (CellBeads®) containing "native" (CB085) or GLP-1 transfected hMSCs (CB087) were stereotactically implanted into the right ventricle of double transgenic mice mutant expressing APP and presenelin-1 protein (APPswe, PSEN1dEG; JACKSON LAB) at 27 weeks of age (n = 14 each). After 8 weeks of implantation (i.e. 35 weeks of age), brains of 4 animals per group were processed for histological assessment using Antibodies against Aβ40/42 (polyclonal; US BIOLOGICAL), glial fibrillary acidic protein (GFAP polyclonal, DAKO) and the microglial marker CD11b (monoclonal; BIOMOL). The remaining brains were used for Aβ40/42 ELIZA. N= 7 35-36 weeks old Tg-mice provided the age-matched early-onset AD controls.

Results

Total counts of Aβ40/42 positively stained plaques assessed in the frontal cortex were reduced in the animals with GLP-1 transfected CellBeads® implants when compared to the "native" stem-cell group and the control:107 ± 24 (GLP-1 hMSCs) vs. 165 ± 44 ("native" hMSCs) vs. 140 (control, n = 1); $p = 0.07$ (t-test of GLP-1 vs. "native" hMSCs). Likewise, the number of reactive astrocytes (> three GFAP positively stained processes) measured in the dentate gyrus of the hippocampus showed a tendency towards a lower count in GLP-1 CellBeads® mice. Morpho-

metric analysis of CD11b positively stained particles per cortical area (%) showed most striking evidence in group differences: animals with GLP-1 transfected CellBeads® showed a significant reduction of microglial immunoreactivity against age-matched AD control: 0.28 ± 0.14% vs. 0.58 ± 0.05% (p = 0.02, t-test). "Native" CellBeads® showed a reduced but not significant change in the microglial response.

Conclusion

GLP-1 producing stem cells encapsulated in alginate have lowered Aβ40/42 load in a mouse model of early-onset AD, which corresponded to a significant down-regulation of specific microglial-type changes in that model.

References

1. Perry T, Lahiri DK, Sambamurti K, Chen D, Mattson MP, Egan JM, Greig NH: **Glucagon-like peptide-1 decreases endogenous amyloid-beta peptide (Abeta) levels and protects hippocampal neurons from death induced by Abeta and iron.** *J Neurosci Res* 2003, **72:**603-612.