P 362 IN VIVO GENE DELIVERY TO THE CNS USING A NOVEL INTEGRIN TARGETING MULTIFUNCTIONAL PROTEIN

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Gene delivery strategies have been developed with the purpose of modulating glial reactivity and provide neuroprotection. Modified viruses are the most widely used strategy although they present long term application restrictions as they can induce toxicity, inflammation and demyelination. In the present study, an alternative approach to the viral mediated gene transfer to the CNS has been explored. A chimeric beta-galactosidase multifunctional vector was used, exploiting the beta-galactosidase intrinsic endosome escaping property and its easy production profile. Moreover, the vector has been modified to display two heterologous domains: a DNA-condensing poly-L-lysine motif and a cell internalization viral ligand (RGD) for alfaVbeta3 integrin. The transfecting efficiency of this vector carrying green fluorescent protein (GFP) as reporter gene was evaluated in vivo by either intracerebral or intravenous injection in postnatal day nine and adult rats. Animals injected with naked DNA encoding GFP were used as control. Our results showed that direct intracerebral injection of the vector into the sensorimotor cortex caused local GFP expression after 24 hours, that remained for at least 7 days and was higher than in DNA-injected controls. This vector was capable of targeting both neurons and glial cells. Preliminary results showed no significant secondary inflammatory reactions during the first week after the injection of the vector alone. Moreover, when a cortical excitotoxic injury was performed before vector injection, the transgene expression became widespread, covering the entire lesioned area. Intravenous vector administration showed GFP expression in the postnatal but not adult rat brain. In conclusion, this non-viral approach of gene transfer to the brain represents a promising strategy for gene therapy as it provides a safe transitory (local or widespread) transgene expression in neurons and glia, presumably devoid of secondary inflammation and demyelination. Supported by: DGESPB98-0892, la Caixa and BIO98-0527. Fellowship to H.P. by AECI and to A.A. by MEC.