Neuroprotective and neurodegenerative effects of the chronic expression of TNF in the substantia Nigra of adult mice
Pitossi, F.; Paolo, N. D.; Schöneberg, A.; Depino, A.; Chertoff, C.; Ferrari, C.; Pfinzenmaier, K.; Podhajcer, O.; Eisel, U.

Published in:
Journal of Neurochemistry

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2003

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 15-10-2020
**Colloquium C06: Gene Transfer to the Nervous System: From Basic Mechanisms to Novel Therapeutics**

**C06-01**
Gene therapy for nervous system repair
H. D. Shine
Baylor College of Medicine, Houston, TX, USA

Using experimental models of neurotrauma, several laboratories have demonstrated the efficacy of neurotrophic factors (NFs) to protect neurons from death and to support axonal regeneration. These observations raised the possibility that NFs might be effective in treating neurotrauma and neurodegenerative diseases in humans. However, clinical applications of NFs have been restricted as systemic delivery of NFs at doses sufficient to reach therapeutic concentrations and to overcome their short half-lives cause adverse effects. These limitations would be overcome if NFs were continually expressed at the target site. We tested whether local expression of NFs would induce axonal regeneration in a model of neural injury. The cortical spinal tract (CST) in rats was lesioned unilaterally at the level of the hindbrain and Neurotrophin-3 (NT-3) was expressed locally in the spinal cord either by retrograde delivery of the vector from the sciatic nerve. Axons were observed growing from the unlesioned CST across the midline to the denervated side. Interestingly, axons did not cross the midline if the CST was not lesioned suggesting that the effect of NT-3 was dependent upon trauma-induced signals. These data demonstrate that local expression of NFs will induce and support axonal regeneration in a circumscribed area after injury without adverse effects and suggest that a therapy based upon this strategy may overcome the limits of systemic NF delivery for SCI.

**Acknowledgements:** Supported by NIH grant NS35280 and Mission Connect of the TIRR Foundation.

**C06-02**
The neuroimmunology of viral vectors for gene transfer: a rational approach to neurological gene therapy
P. R. Lowenstein and M. G. Castro
Gene Therapeutics Research Institute, Cedars-Sinai Medical Center, and David Geffen School of Medicine, University of California Los Angeles, CA, USA

Vectors, such as adenovirus and lentivirus-derived vectors, are powerful tools to transfer genes into the brain, for either basic science or therapeutic aim. Various types of vectors have now been shown to allow up to 12–18 months of stable transgene expression in the brain. However, injection of viral vectors into the brain and molecular mechanisms used by cells of the adaptive immune system to abolish transgene expression in the brain have not yet been completely elucidated. Understanding these phenomena is complicated by the so called ‘brain immune privilege’. This presentation will discuss the interactions of viral vectors with both the innate and adaptive immune response, and propose how an understanding of the basis for the brain’s immune privilege can aid in the development of gene therapies for brain disorders, both for chronic neurodegeneration, such as Parkinson’s disease (PD), and for acute trauma, such as spinal cord injury. The cortical spinal tract (CST) in rats was lesioned unilaterally at the level of the hindbrain and Neurotrophin-3 (NT-3) was expressed locally in the spinal cord either by retrograde delivery of the vector from the sciatic nerve. Axons were observed growing from the unlesioned CST across the midline to the denervated side. Interestingly, axons did not cross the midline if the CST was not lesioned suggesting that the effect of NT-3 was dependent upon trauma-induced signals. These data demonstrate that local expression of NFs will induce and support axonal regeneration in a circumscribed area after injury without adverse effects and suggest that a therapy based upon this strategy may overcome the limits of systemic NF delivery for SCI.

**Acknowledgements:** Supported by NIH grant NS35280 and Mission Connect of the TIRR Foundation.

**C06-03**
Neuroprotective and neurodegenerative effects of the chronic expression of TNF in the substantia nigra of adult mice
F. Pitossi, N. Di Paolo, A. Schöneberg, A. Depino, C. Chertoff, C. Ferrari, K. Pfinznermaier, O. Podhajcer* and U. Eiselt†
*Foundation Leloir Institute, CONICET-UBA, Buenos Aires, Argentina; †Institut für Zellbiologie und Immunologie, Stuttgart, Germany

Activation of microglia and induction of cytokines such as Tumor necrosis factor alpha (TNF) in the substantia nigra (s.n.) have been observed in animal models and patients with Parkinson’s disease (PD). However, it is unclear whether this microglial activation could be functional to remove cellular debris after neuronal death or could be triggering, propagating or delaying the death of dopaminergic neurons. We have generated conditional knock-in mice in which a TNF transgene is under the control of the endogenous engrailed promoter (which directs protein expression mainly to the s.n.). In these mice, constitutive TNF expression is reduced by an interfering cassette that is flanked by loxP sequences. Injection of adenoviral vectors expressing CRE (AdCRE) in the s.n. resulted in removal of the interfering cassette. In addition, s.n.-specific TNF up-regulation was seen in the AdCRE-injected knock-in mice but not in control animals. Using this combination of techniques, we showed that while chronic up-regulated TNF expression induced progressive neuronal loss, lower TNF levels were neuroprotective in the s.n. in the 6-OHDA model of PD. These data suggest a dual role of the chronic expression of TNF in the s.n. In addition, the progressive neurodegenerative effect of TNF per se in the s.n. provided us with a new animal model of PD.

**Acknowledgements:** Grants from René Barón, Volkswagen, Antorchas Foundations, CONICET and DAAD.