ABSTRACT

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The efficacy of NGF-secreting primary monocytes as therapeutic delivery vehicles in a cognitively impaired cholesterol rat model

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Background: Nerve growth factor (NGF) serves an important role in the maintenance and survival of cholinergic neurons in the basal forebrain and proves the most potent neuroprotective molecule against cholinergic neurodegeneration, a typical hallmark of Alzheimer’s disease (AD). However, delivery of this factor to the brain remains difficult. The aim of the present study was (1) to test different transfer methods to generate NGF-secreting monocytes and (2) to evaluate the effects of intravenously (i.v.) applied primary monocytes alone or NGF-secreting monocytes in a cholesterol-induced cognitively impaired Brown Norway rat model.

Methods: Here, we assessed several different transfer methods (electroporation, nucleofection, viral transfer, Biopporter protein loading) in order to generate NGF-secreting monocytes. Monocytes alone or NGF-secreting monocytes were delivered in vivo via the dorsal penis vein in cholesterol-fed Brown Norway rats. Cognitive performance, including spatial learning and memory, was evaluated by an 8-arm maze. Neuroprotection was assessed by quantifying choline acetyltransferase (ChAT) neuron survival in the nucleus basalis of Meynert as well as measuring cortical NGF and acetylcholine (ACh) levels. Neuroinflammation was analysed by measuring cytokine and chemokine levels (MCP-1, MIP-2, TNF-α, IL-1β) in brain lysates and by immunohistochemical evaluation of microglia staining in cortical regions.

Results: In this study, we demonstrate that lentiviral vectors and Biopporter protein delivery can successfully transduce primary rat monocytes and produce effective NGF secretion. Furthermore, our results indicate that NGF is bioactive and that Biopporter-loaded monocytes do not exhibit functional disruptions (i.e. differentiation and phagocytosis potential). Following two months of monocyte i.v. treatment, animals treated with monocytes alone displayed significantly enhanced ACh, slightly enhanced ChAT neuron survival, and significantly reduced microglia activation. These findings, however, did not translate into a marked effect on cognitive performance. Animals which received NGF-loaded monocyte injections demonstrated significantly better cognitive performance compared to monocytes alone and significantly elevated ChAT neuron survival. However, these animals did show significantly elevated staining for microglia activation. Most importantly, we demonstrate that repeated i.v. injection of primary monocytes does not result in elevated release of proinflammatory cytokines and chemokines in the brain.

Discussion: Taken together, our data suggests that i.v. infusion of monocytes could serve as a potent cell-based therapy for neurodegenerative diseases. However, further studies are needed in order to evaluate the efficacy of these cells in counteracting cognitive impairments and disease pathogenesis in transgenic AD mice. This work has been published in [1,2,3].

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References