Ocular Nerve Growth Factor Administration Modulates Brain-derived Neurotrophic Factor Signaling in Prefrontal Cortex of Healthy and Diabetic Rats

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SUMMARY

Aims: Nerve growth factor (NGF) eyedrops (ed-NGF) activate brain neurons, stimulate growth factors, including brain-derived neurotrophic factor (BDNF), and exert neuroprotection in the forebrain of streptozotocin-induced diabetic rats (STZ rats). In this study, the effects of ed-NGF on BDNF signaling in the prefrontal cortex (PFC) were explored in healthy and STZ diabetic rats, in which cortical neuronal and axonal loss, and altered circulating BDNF associated with depressive phenotype are also described. Methods: STZ and healthy (CTR) adult rats received ed-NGF twice a week for 2 weeks. Depressive phenotype was identified by force swimming test (FST). Proteins extracted from PFC were processed for ELISA and Western blot analyses to measure the expression of BDNF, proBDNF, and their receptors and intracellular signals. Results: ed-NGF treatment modulates BDNF pathway in PFC and normalizes the STZ-induced BDNF alterations by stimulating TRK-mediated survival mechanism. A decreased latency in FST was also found in STZ rats, while no change was observed comparing CTR + NGF and STZ + NGF with CTR. Conclusion: The present data confirm the capacity of ed-NGF treatment to affect brain neurons and lead to brain damage recovery by activating protective and remodeling pathways triggered by BDNF. We suggest that the ed-NGF-induced changes in BDNF signaling might influence the manifestation of depressive phenotype in diabetic rats.

Introduction

Nerve growth factor (NGF) is an essential neurotrophin acting on both mature and immature neuronal cells during the entire life span [1,2], exerting neuroprotective/regenerative actions in the brain when intracerebrally injected. NGF administered as eyedrops on ocular surface (ed-NGF) also produces its biological actions on the retina, optic nerve, and primary visual brain areas, as well as on a wide range of forebrain regions, including the frontal and occipital cortex [3]. Mature neuronal cells and precursors respond to ed-NGF treatment, also by producing and/or releasing neurotransmitters, cytokines, growth factors, including the cognate neurotrophin brain-derived neurotrophic factor (BDNF) in both healthy [4-6] and pathological conditions [4,7,8].

Recently, ed-NGF has been demonstrated to counteract brain neurodegeneration in a rat model of diabetic encephalopathy induced by streptozotocin (STZ) by stimulating the survival of forebrain cholinergic neurons and neuronal precursors, and activating neurogenesis in the subventricular germinal area [4,9].

Besides affecting cholinergic areas, STZ is also reported to produce axonal degeneration and demyelination in the cortex of rats as early as 4 weeks after injection [10]. Accordingly neuronal cell death in the prefrontal cortex (PFC) is associated with the manifestation of depressive phenotype in STZ mice [11]. A correlation between onset of depressive-like behavior and altered structure and neurotransmission in PFC has also been demonstrated in STZ-treated mice [12], supporting the observed diabetes and depression comorbidity in patients [13]. In this context, this study addresses possible protective effects of ed-NGF against diabetic encephalopathy rats, with a focus on the neurodegenerative process occurring in PFC.

Specifically, we investigated the relationship between STZ and ed-NGF effects on PFC levels of molecules involved in BDNF-regulated pathways. Our working hypothesis is based on the following evidence: (1) BDNF is produced in the PFC and regulates cortical interneuronal activity [14], thus contributing to the modulation of behavioral functions; (2) BDNF plays a critical role in mood disorders, being downregulated in depression, even in association