Behavioural Brain Research 221 (2011) 515–526

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

# The cholinergic system, nerve growth factor and the cytoskeleton

Grazyna Niewiadomska*, Anna Mietelska-Porowska, Marcin Mazurkiewicz

*Laboratory of Preclinical Studies in Neurodegenerative Diseases, Department of Neurophysiology, Nencki Institute, Warsaw, Poland*

ARTICLE INFO

*Article history:*
Received 7 January 2010
Accepted 10 February 2010
Available online 16 February 2010

*Keywords:*
Brain cholinergic neurons
Nerve growth factor
NGF receptors
Cytoskeleton
Neuronal transport
Neurotrophic signaling
Tau protein
Neurodegenerative diseases
Tauopathies

ABSTRACT

Cholinergic neurons of the basal forebrain provide the major cholinergic innervation to the cortex and hippocampus, and play a key role in memory and attentional processes. Dysfunction of basal forebrain cholinergic neurons (BFCN) is a cardinal feature of Alzheimer's disease (AD) and correlates with cognitive decline. Survival of BFCN neurons depends upon binding of nerve growth factor (NGF), which is synthesized and secreted by cells in the cortex and hippocampus, with high-affinity (TrkA) and low-affinity ($p75^{NTR}$) neurotrophin receptors produced within BFCN neurons. NGF released from target cells activates TrkA on axon terminals and triggers activation of PI3K/Akt, MEK/ERK, and PLCγ (phospholipase C) signaling pathways. The signal then travels retrogradely along axon to cell body to promote neuronal survival. However, the nature of the retrograde signal remains mysterious. $p75^{NTR}$ receptors could mediate a fundamentally different signaling pathway leading to apoptic cell death. Dysfunction of NGF and its receptors has been suggested to underlie the selective degeneration of the BFCN in end stage Alzheimer disease. In this regard, NGF, the founding member of the neurotrophin family, has generated great interest as a potential target for the treatment of AD. This review focuses on NGF-cholinergic dependency, NGF/receptor binding, signal transduction, retrograde transport, regulation of specific cellular endpoints, and the potential involvement of cytoskeleton dysfunction in defected NGF signaling.



**Contents**



* Corresponding author. Tel.: +48 225892409; fax: +48 228225342.
*E-mail address:* g.niewiadomska@nencki.gov.pl (G. Niewiadomska).

0166-4328/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2010.02.024

## 1. Brain cholinergic neurons and nerve growth factor (NGF)

The basal forebrain cholinergic neurons (BFCN) are largely comprised of the nucleus basalis magnocellularis (NBM), the horizontal and vertical diagonal bands of Broca (HDB and VDB respectively), and the medial septal nucleus (MS). Cholinergic neurons within the nucleus basalis and the septal diagonal band complex provide the major source of cholinergic innervation to the cerebral cortex and hippocampus, respectively, and play a key role in memory and attentional function. While neurons situated at the MS typically project into the hippocampus, those in NBM provid cholinergic innervation to the amygdala and remaining portions of the cortical mantle (for review, see [1,2]). Cholinergic neurons in the CNS undergo complex changes during normal aging. In recent years, considerable attention has focused on the neurotrophins and, in particular, nerve growth factor (NGF), as potential maintenance factor for cholinergic-neuron function, and as therapeutic agents for use in a variety of neurodegenerative disorders including Alzheimer's disease. The brain cholinergic neurons from the neonate to the aged are highly dependent on the offer of NGF. The embryonic development of the BFCN is highly dependent on the expression of both NGF and its receptors. The trophic dependence of cholinergic neurons on NGF remains critical even in the mature and fully differentiated CNS. Experimental evidence indicates that within the adult CNS, NGF plays a role in the maintenance of the cholinergic neurons transmitter and morphological phenotype but not in cell survival [3,4] (Fig. 1).

NGF is a member of the neurotrophin (NT) family. Other mammalian proteins of this family include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin 4/5 (NT-4/5). NGF plays a key role in stimulation, survival and phenotypic maintenance of adult BFCNs [5]. It is synthesized in the cortex and the hippocampus and is retrogradely transported to BFCNs cell bodies triggering the process leading to the maintenance of normal cellular functions and morphology. NGF has been shown to upregulate several cholinergic markers, i.e. ChAT activity, gene expression and protein levels [6], acetylcholine synthesis and release [7], and the expression of vesicular acetylcholine transporter (VAChT) [8]. Substantial evidence suggests that NGF regulates both the cell size of basal forebrain cholinergic neurons and the extent of their terminal arborization [9]. The endogenous NGF plays a critical role in cholinergic synaptic remodeling in the adult CNS. It was observed that the number of cortical cholinergic synapses depends on the continuous supply of NGF, as the use of anti-NGF monoclonal antibodies or TrkA receptor antagonists produces a depletion of pre-existing cholinergic buttons [10]. NGF-producing cells are present in the cortical target regions of basal forebrain cholinergic neurons. Most such cells are neurons, including pyramidal neurons, though glial cells are occasionally found to contain NGF [11]. In the hippocampal formation, pyramidal and dentate granule neurons express NGF. Additionally, subpopulations of GABAergic interneurons in hippocampus and basal forebrain also synthesize NGF [12]. NGF expression in hippocampus is regulated by neuronal activity; increases are caused by glutamatergic and cholinergic neurotransmission, and decreases are caused by GABAergic neurotransmission [13]. Neuronal NGF expression *in vivo* is markedly upregulated by seizures, forebrain ischemia, marked hypoglycemia, and tissue injury [14]. Among glial cells, NGF is produced throughout the CNS by astrocytes and microglia, and NGF expression in both cell types is markedly upregulated by local tissue injury, inflammation, cytokines, and bacterial lipopolysaccharide [15].

In addition to NGF effects on normal neuron function, NGF and its receptors have been proposed to contribute to the deleterious effects of old age and degenerative diseases in the nervous system which are associated with reduced neurotrophic support [16]. Recently, a novel way in which neurotrophins could contribute to neurodegeneration has been suggested. In contrast to the well-known neurotrophic functions of the mature form of NGF, its precursor pro-NGF has recently been shown to be abundant in the adult brain and in the brains of patients with Alzheimer's disease. Pro-NGF has been shown to be neurotoxic when bound in a heterotrimer with the p75 receptor and the receptor sortilin. Interestingly, it was shown that sortilin levels increase in aged central and peripheral neurons, perhaps making the neurons more vulnerable to age-related increases in pro-NGF. Therefore, it was proposed that increased pro-NGF in targets combined with increased sortilin expression in projecting neurons contributes to age-related neuronal atrophy and degeneration [17].

A number of *in vivo* studies have demonstrated that age-related dysfunction of cholinergic system might be ameliorated by treat-

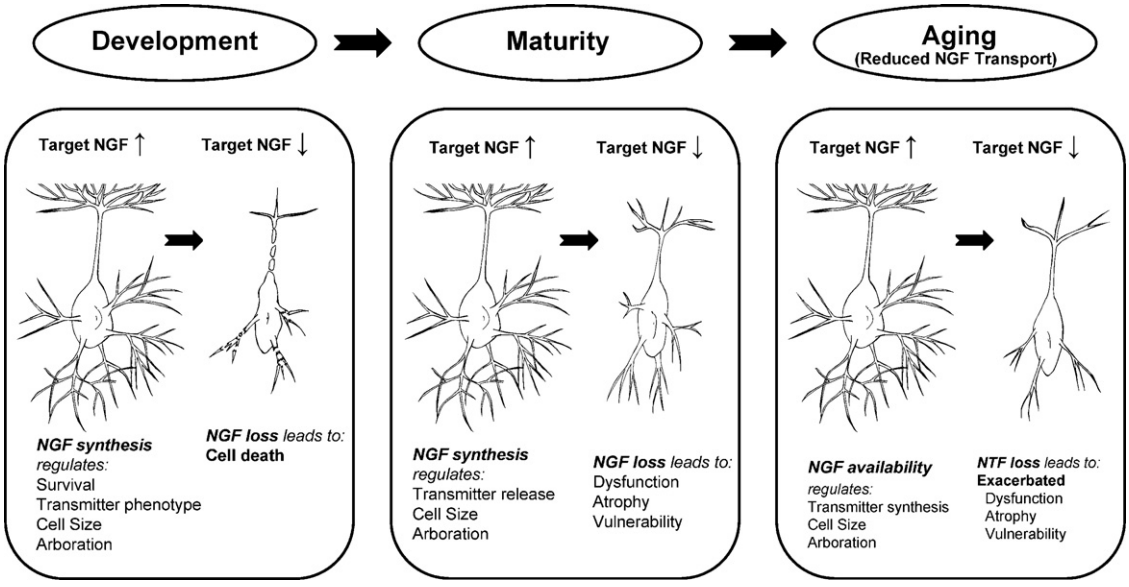


**Fig. 1.** NGF-mediated neuron-target interactions. Several important mechanisms of the cholinergic system development and maturity are depending on the NGF availability in targets of the cholinergic projection.
Adopted from Sofroniew et al., 1993 [5].