Free Radical Biology and Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

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

Review Article

Dysregulation of neurotrophin signaling in the pathogenesis of Alzheimer disease and of Alzheimer disease in Down syndrome☆

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ARTICLE INFO

Keywords:
Neurotrophin
Signaling endosome
Down syndrome
Alzheimer's disease
Endosome enlargement
Axonal transport deficit
Degeneration

ABSTRACT

Neurotrophic factors, including the members of the neurotrophin family, play important roles in the development and maintenance of the nervous system. Trophic factor signals must be transmitted over long distances from axons and dendrites to the cell bodies of neurons. A mode of signaling well suited to the challenge of robust long distance signaling is the signaling endosome. We review the biology of signaling endosomes and the "signaling endosome hypothesis". Evidence for disruption of signaling endosome function in disorders of the nervous system is also reviewed. Changes in endosome structure in Alzheimer disease (AD) and Down syndrome (DS) are present early in these disorders. Data for the APP products responsible are reviewed and the consequent changes in signaling from endosomes discussed. We conclude by pointing to the need for additional studies to explore the biology of signaling endosomes in normal neurons and to elucidate their role in the pathogenesis of neurodegeneration.

1. Introduction

Alzheimer's disease (AD) is a fatal neurodegenerative disorder, characterized by progressive memory loss and cognitive decline with dementia [1,2]. Down syndrome (DS), the most common genetic cause of AD, is due to trisomy for all or part of a third copy of chromosome 21. Almost all adults with DS develop AD-like neuropathology by the age of 40, a disorder termed AD in DS (AD-DS) [3,4]. The evidence is compelling that increased gene dose for APP is necessary for AD-DS [5–7], but the underlying mechanism that links APP gene dose to neurodegeneration is unknown.

Our studies point to a role for increased levels of APP gene products in disrupting the formation and trafficking of signaling endosomes [8]. The signaling endosome is a recently discovered organelle in which a neurotrophin, bound to its activated receptor, signals robustly to the cytosol. Importantly, signaling endosomes are transported within neurons to carry neurotrophic signals from axons and dendrites to distant cell bodies, in so doing supporting developing and mature neurons [9–11]. In this article, we review the biology of the neurotrophic signaling endosome and highlight evidence pointing to impairment of neurotrophic signaling from endosomes as contributing to pathogenesis in AD and AD-DS. We suggest future directions for research to explore the potential mechanisms and significance of disruption of neurotrophic signaling in AD and AD-DS.

2. Neurotrophic factors: essential for the developing and mature nervous system

Growth factors (also called trophic factors) are polypeptides that bind to specific cell membrane surface receptors to initiate signaling pathways that regulate diverse processes, including proliferation, survival, migration and differentiation. The neurotrophic factors constitute a class of trophic factors that act on cells of the peripheral and central nervous system (CNS). Prominent neurotrophic factors include the members of the neurotrophin (NT) family, the glial cell-line derived neurotrophic factor family and the ciliary neurotrophic factor family. Neurotrophic factors are best characterized with respect to their regulation of neuronal functions in the developing and mature nervous system [12–16].

The NT family consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT4). Each binds and activates a tropomyosin receptor kinase(s) (Trks) (NGF to TrkA, BDNF and NT4 to TrkB, NT3 to TrkC and to TrkA), to exert trophic effects [12,14,17]. All the NTs also bind to the p75 neurotrophin receptor (p75), to mediate cellular responses largely distinct from the classical trophic effects registered for Trk activation [12,14,17]. Activation of NT receptors initiates several downstream signaling pathways, including the mitogen-activated kinase (MAPK) pathway, the phosphoinositol-3-kinase (PI3 K) pathway and the

☆ This article is part of a special issue entitled: Down Syndrome: From Development to Adult Life to Alzheimer Disease, edited by Allan D. Butterfield and Marzia Perluigi.

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http://dx.doi.org/10.1016/j.freeradbiomed.2017.10.341
Received 11 August 2017; Received in revised form 5 October 2017; Accepted 10 October 2017

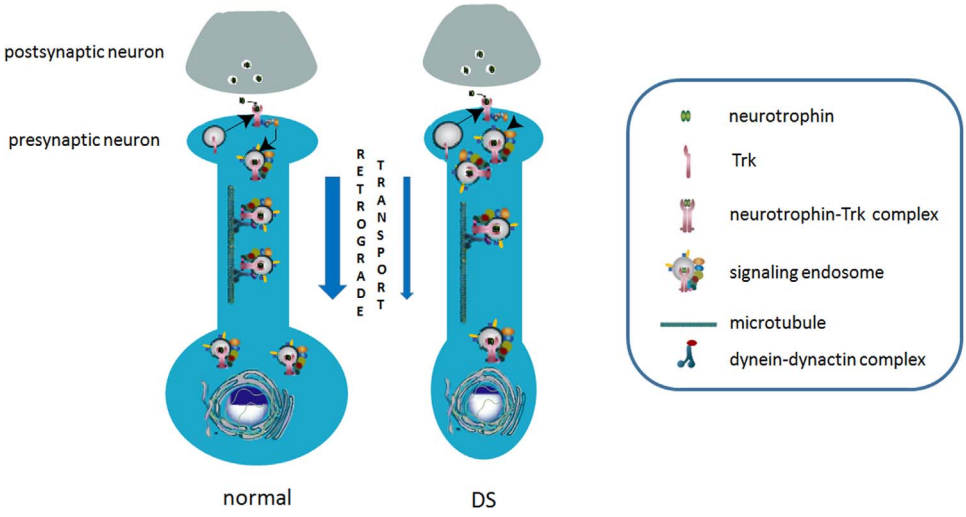

Fig. 1. Endosomal dysfunction in DS compromises signaling of neurotrophic factors. Neurons derive an important source of neurotrophic support from postsynaptic neurons. The latter synthesize and release neurotrophin molecules which then diffuse to presynaptic neurons where they bind to specific cognate receptors on surface membranes. Signaling endosomes are formed when the neurotrophin/receptor complex undergoes endocytosis. This remarkable organelle carries on its cytosolic surface activated isoforms of the downstream signaling pathways activated by the neurotrophin/receptor complex. Once created, signaling endosomes convey signaling to all parts of the presynaptic neuron, including the synapse, the axon, the cell body, and in some cases also dendrites. In normal, healthy neurons, there is a steady flow of signaling endosomes from synapses to cell bodies via dynein-mediated retrograde transport in axons. Long-distance axonal transport allows for the postsynaptic neuron to influence both somal and nuclear events in the presynaptic neuron that serve to ensure the structure and function of the presynaptic neuron, including its ability to synaptically partner with the postsynaptic neuron. Due to increased activation of Rab5, in AD and AD-DS there is enlargement of early endosomes, a change that is correlated with changes in trafficking of signaling endosomes. Though the mechanisms by which APP and its products act are yet to be defined, existing data point to two consequences of disrupted trafficking of signaling endosomes: increased neurotrophin signaling from endosomes in distal axons and deficient transport of signaling endosomes to cell bodies. Studies to explore these changes will be important for understanding their biological significance. Existing data support the view that decreased transport of signaling endosomes to cell bodies results in decreased trophic signaling with resulting atrophy, a hallmark of neurodegeneration in AD and AD-DS. As yet undefined are which signaling pathways are impacted by reduced delivery of signaling endosomes to cell bodies. Nevertheless, that such deficits are present is data showing that p-CREB levels were reduced in neurons overexpressing C99 [62].

phospholipase C-γ (PLCγ) pathway [18,19]. Activation of these pathways, and integration of their signals, is responsible for the diverse and potent effects of NTs on neuron structure and function [18,19].

3. The biology of long distance signaling in neurons

NT-induced signaling in neurons is carried out in the context of a complex cellular anatomy in which cell bodies receive signals from elaborate dendritic networks as well as from axons projecting to distant synaptic partners. This architecture poses formidable challenges for delivering NT signals generated at cell surface receptors distant from the cell body. Methods must exist to support transmission of signals robustly and faithfully over long distances. One mechanism for transmitting the signals generated by NT/Trk complexes is via endosomes that carry the active signaling complex [9–11]. Following NT release from target cells and tissues, an NT binds and activates its cognate Trk receptor at the cell surface. The internalization of the activated complex via endocytosis creates the “signaling endosome”, an organelle that can then be trafficked to the cell body via dynein-based transport (Fig. 1) [11]. Though the signaling endosome is not uniquely found in neurons, its discovery was facilitated by recognizing the need for means by which to convey over long distances the NT signaling required for establishing and maintaining communication between geographically distant neuronal compartments.

4. Structure and biology of signaling endosomes: the signaling endosome hypothesis

The signaling endosome contains not only the internalized and activated NT/Trk complex, but also carries on its cytosolic surface the activated isoforms of many of the proteins responsible for signaling through the MAPK, Akt and PLCγ pathways [15]. Justifying its name, the signaling endosome has been shown to signal to downstream substrates. Several lines of evidence support this. First, following NGF treatment, isolated clathrin-coated vesicles contain NGF bound to TrkA receptor together with activated components of the MAPK pathway [20–22]. Second, NGF/TrkA containing endosomes and active kinases of the MAPK signaling pathway are present in the axons and cell bodies of dorsal root ganglion (DRG) neurons where they colocalize with an early endosome marker [23]. Third, cellular fractionation of endosomes formed in vivo showed cofractionation with early endosomes of the activated TrkA receptor and components of the MAPK pathway [23]. Finally, isolated endosomes were able to transmit the MAPK signal in an in vitro kinase assay [23]. These data combine to demonstrate that continued signaling arises from the NT/Trk endosome during its transport from neuronal processes to the cell body [20,23,24]. Although there are additional models for long distance NT signaling, including possibly ligand-independent NT signal transduction [25], a large and compelling body of evidence strongly support the “signaling endosome” hypothesis [20,23,24,26]. Excellent reviews speak to the formation of signaling endosomes, their composition and loading onto motor proteins, and initiation and regulation of transport [9,27].

Once created the signaling endosome is loaded onto dynein motors for transport to the cell body where the NT/Trk signaling induces changes in both the cytosol and nucleus to support many aspects of neuronal structure and function [9–11,15]. Given evidence of persistent signaling from NT/Trk containing endosomes, the possibility exists that signaling from endosomes informs all of the compartments through which it moves in transit to the cell body. This facet of signaling endosome biology is yet to be adequately explored but serves as an important target of ongoing studies aimed at determining the local impact of NT/Trk signaling. The extent to which signaling endosomes support signaling from ligand/receptor complexes other than NT/Trk complexes is less well studied, but data support the view that this mode of signaling is widely used. Thus, endosome-based signaling also appears to define an important common platform for signaling transduction from receptor tyrosine kinases other than the Trks, including the receptors for epidermal growth factor and transforming growth factor. Remarkably, other types of receptors and protein complexes may also signal from endosomes, including G-protein-coupled receptors and ion channel [28–30].

5. Diversity in signaling endosomes

Both clathrin-dependent [20] and independent endocytosis, including Pincher-mediated endocytosis [31], have been shown to mediate internalization of the NT/Trk complex into endosomes. The process is regulated and coordinated by various Rab small GTPases and other