

Review

# Effects of Reactive Oxygen and Nitrogen Species on TrkA Expression and Signalling: Implications for proNGF in Aging and Alzheimer's Disease

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**Abstract:** Nerve growth factor (NGF) and its precursor form, proNGF, are critical for neuronal survival and cognitive function. In the brain, proNGF is the only detectable form of NGF. Dysregulation of proNGF in the brain is implicated in age-related memory loss and Alzheimer's disease (AD). AD is characterized by early and progressive degeneration of the basal forebrain, an area critical for learning, memory, and attention. Learning and memory deficits in AD are associated with loss of proNGF survival signalling and impaired retrograde transport of proNGF to the basal forebrain. ProNGF transport and signalling may be impaired by the increased reactive oxygen and nitrogen species (ROS/RNS) observed in the aged and AD brain. The current literature suggests that ROS/RNS nitrates proNGF and reduce the expression of the proNGF receptor tropomyosin-related kinase A (TrkA), disrupting its downstream survival signalling. ROS/RNS-induced reductions in TrkA expression reduce cell viability, as proNGF loses its neurotrophic function in the absence of TrkA and instead generates apoptotic signalling via the pan-neurotrophin receptor p75<sup>NTR</sup>. ROS/RNS also interfere with kinesin and dynein motor functions, causing transport deficits. ROS/RNS-induced deficits in microtubule motor function and TrkA expression and signalling may contribute to the vulnerability of the basal forebrain in AD. Antioxidant treatments may be beneficial in restoring proNGF signalling and axonal transport and reducing basal forebrain neurodegeneration and related deficits in cognitive function.

**Keywords:** oxidative stress; nitrative stress; neurotrophin; p75<sup>NTR</sup>; basal forebrain; retrograde transport



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## 1. Nerve Growth Factor Receptors and Signalling

Mature nerve growth factor (NGF) is a 13.2 kD protein that is essential for cell survival, synaptic plasticity, neurite outgrowth, and differentiation [1,2]. NGF binds to the tyrosine kinase receptor, TrkA, to elicit its neurotrophic functions [1,3]. NGF-induced TrkA activation initiates three main signalling cascades, the phosphatidylinositol-3-kinase (PI3K)-Akt pathway, the Ras-mitogen activated protein kinase-extracellular signal regulated kinase (Ras-MAPK-ERK) pathway, and the phospholipase C-gamma (PLC- $\gamma$ ) pathway [4–7]. Activation of the PI3K-Akt pathway is required for NGF-induced cell survival, while both Ras and PLC- $\gamma$  signalling contribute to NGF-induced neurite outgrowth [4,8,9]. In addition to activation of the ERK signalling cascade, NGF activates the p38 MAPK pathway downstream of Ras [10]. Both of these pathways induced by NGF contribute to activating phosphorylation of the transcription factor cAMP-response element binding protein (CREB) at serine-133 [10]. CREB regulates various genes associated with beneficial functions including neurogenesis, neuronal survival, synaptic plasticity, and cognitive function [11].

Mature NGF also binds with low affinity to the pan-neurotrophin receptor, p75<sup>NTR</sup> [1]. In the absence of TrkA, NGF-induced activation of p75<sup>NTR</sup> induces apoptosis by activating

ceramide and c-Jun N-terminal kinase (JNK) signalling [1,7,12]. However, in the presence of TrkA, p75<sup>NTR</sup> enhances the neurotrophic functions of NGF by increasing the affinity of NGF for TrkA, increasing NGF/TrkA internalization, and inducing signalling via Akt to increase cell viability [1,7,13]. Activation of TrkA inhibits the apoptotic signalling of p75<sup>NTR</sup> via the PI3K-Akt and Ras-MAPK-ERK pathways, which inhibit apoptotic signalling factors and activate anti-apoptotic factors, respectively [7].

The NGF gene contains two different promoters, and the resulting transcripts can be alternatively spliced to produce two major and two minor mRNA sequences [14,15]. Translation of NGF from the two major transcripts results in preproNGF species of 34 kDa and 27 kDa [16]. Following removal of the signal peptide in the endoplasmic reticulum, 32 and 25 kDa proNGF species remain [14,17–20]. These species can be further processed by various proteases to produce the mature, 13.2 kDa form of NGF [21–23]. However, in the human, rat, and mouse brain, proNGF is the predominant species, while mature NGF is not detected [24]. ProNGF exists as a 64 kDa dimer that has similar biological activity to mature NGF, although with lower potency [25,26]. Several studies indicate that proNGF binds to TrkA, albeit more weakly than mature NGF, and elicits TrkA phosphorylation and activation of downstream signalling factors including MAPK, ERK1/2, and Akt [25,27–29]. There is extensive literature indicating that proNGF exhibits a similar neurotrophic function to mature NGF in its ability to promote cell survival and neurite outgrowth [25,27–33]. Several of these studies utilized cleavage-resistant proNGF mutants and performed experiments in the presence of protease inhibitors to confirm that the observed neurotrophic effects were induced by proNGF rather than its mature form [25,27–29]. In these studies, the lack of proNGF cleavage was also confirmed via Western blot, providing further confidence that proNGF is neurotrophic [25,27–29].

Despite extensive literature supporting the role of proNGF as a neurotrophic factor, other evidence implicates proNGF in apoptosis [21,34]. These contradictory results can be explained by differences in proNGF receptor expression [28]. In the absence of TrkA, proNGF activates apoptotic signalling through p75<sup>NTR</sup>, together with sortilin [21,28,29,34]. However, in the presence of TrkA, proNGF retains neurotrophic activity [25–29]. Therefore, receptor expression is critical in determining the cellular outcome of proNGF activity [28,29,35].

## 2. Basal Forebrain Cholinergic Neurons: Dependence on NGF and Implications in Alzheimer's Disease

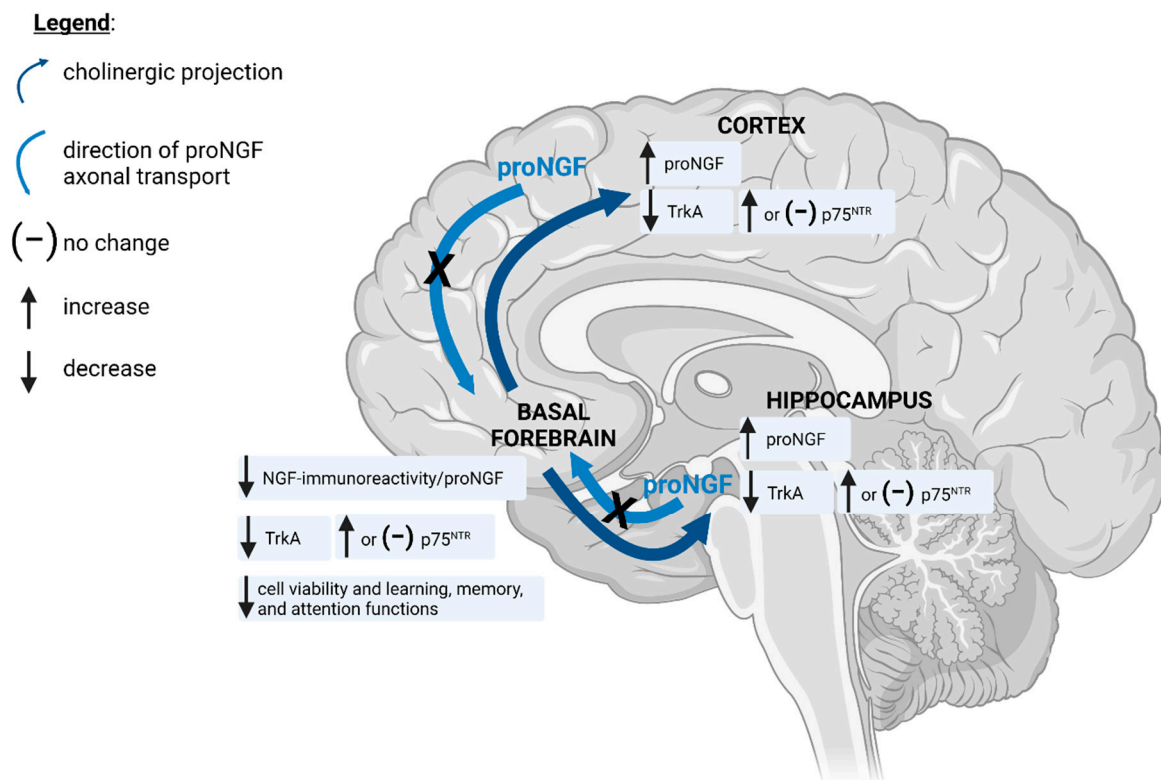
Alzheimer's disease (AD), the most common form of dementia, is characterized by progressive learning and memory deficits and accumulations of amyloid-beta and hyperphosphorylated tau proteins [36]. One brain area that is particularly vulnerable to AD is the basal forebrain [37]. Degeneration of basal forebrain cholinergic neurons (BFCNs), which are critical for learning, memory, and attention, contributes to the cognitive decline seen in aging and AD [38–42]. BFCN degeneration is also a feature of Down's syndrome (DS), a trisomy of chromosome 21 that includes the amyloid precursor protein gene and produces AD-like pathology [43,44].

BFCNs rely on NGF for their survival and function [35,45–51]. Early studies demonstrated the presence of NGF mRNA overlapping with cholinergic subfields within the horizontal limb and diagonal band of Broca within the basal forebrain, suggesting that these neurons supplied their own NGF [52,53]. However, later studies revealed that this NGF was present exclusively within GABAergic, not cholinergic, neurons within these regions [54]. Early in vivo work indicated that fimbria–fornix transection results in BFCN cell death and reduced learning and memory functions, both of which can be rescued by the addition of NGF [51,55]. These observations, coupled with the high levels of NGF present within the cortical and hippocampal targets of BFCNs, suggest that these neurons are reliant on retrograde axonal transport for their supply of NGF [53].

Mature NGF, bound to its receptors on axon terminals, is retrogradely transported from synaptic terminals to cell bodies in signalling endosomes, which contain TrkA and its downstream signalling factors and activate downstream signalling pathways along the

length of the axon and in the cell body [56–60]. Recent evidence indicates that proNGF is also retrogradely transported by neurons in both the central and peripheral nervous systems and is transported in signalling endosomes, similarly to mature NGF [61–63].

The aged basal forebrain exhibits impairments in the retrograde transport of NGF as well as in general axonal transport [64–66]. In AD and DS, NGF immunoreactivity accumulates throughout the cortex and hippocampus and is reduced in the basal forebrain, indicating a deficit in its retrograde transport (Figure 1) [59,67–71]. However, these studies did not differentiate mature NGF from its precursor form, as the molecular weight of the detected proteins was not analyzed. The antibodies used for NGF detection via EIA, ELISA, dot blot, and immunohistochemistry in these studies, directed against mature NGF, also recognize proNGF. More recent studies demonstrate that the previously reported accumulations of mature NGF are actually proNGF rather than its mature form [24,63,72,73]. Similar proNGF accumulations are observed in the cortex of patients with DS, AD, and mild cognitive impairment, as well as in DS and AD rodent models [72–75]. Processing of proNGF to its mature form may be impaired in DS and AD, which may contribute to proNGF accumulation [75–77]. However, the lack of detectable NGF in healthy or diseased brain, the regional specificity of proNGF accumulation and the decreased immunoreactivity in the basal forebrain are highly suggestive of impaired retrograde transport deficits. No differences in the expression of NGF mRNA are observed in the aged or AD brain despite observed increases in NGF-immunoreactive protein in the hippocampus and cortex and decreases in the basal forebrain, supporting the role of retrograde transport [69,78,79]. Furthermore, deficits in proNGF retrograde axonal transport have been reported in BFCNs aged in vitro [35,63]. Similar reductions in the retrograde transport of  $^{125}\text{I}$ -NGF and cholinergic deficits are observed in DS mice and aged rats [59,64]. Thus, retrograde transport of proNGF in BFCNs is impaired in cellular models of aging and in DS and AD animal models and likely also in DS and AD.



**Figure 1.** Alterations in proNGF distribution and receptor expression in aging and Alzheimer’s disease. Basal forebrain cholinergic neurons (BFCNs) send projections widely throughout the cortex and hippocampus. In the healthy brain, BFCNs receive neurotrophic support from these brain areas via retrograde transport of pro-nerve growth factor (proNGF). In aging and Alzheimer’s disease (AD), proNGF accumulates throughout the cortex and hippocampus, with accompanying decreases

in proNGF/NGF-immunoreactive material in the basal forebrain. Decreased tropomyosin-related kinase A (TrkA) levels are observed in the basal forebrain, cortex, and hippocampus, with either increased or no change in levels of the pan-neurotrophin receptor, p75<sup>NTR</sup>. These alterations are associated with BFCN degeneration and loss of learning, memory, and attention in aging and AD. Diagram was created using [BioRender.com](https://www.biorender.com) (accessed on 4 August 2021).

The accumulation of proNGF in the cortex and hippocampus reduces BFCN survival and function. In mild cognitive impairment and early stages of AD, cortical proNGF accumulation is inversely correlated with cognitive scores [72,80]. The accumulation of proNGF in the rat cortex, mimicking the accumulation seen in AD, causes degeneration of the BFCNs that innervate this area, indicated by decreased BFCN soma size and reduced cortical cholinergic innervation and synapses as well as reduced learning and memory [80,81].

Reductions in TrkA expression and signalling are also observed in the AD brain, with either no observed differences or an elevation in p75<sup>NTR</sup> expression (Figure 1) [64,82–88]. Similar reductions in TrkA and no change in p75<sup>NTR</sup> expression are found in animal and cellular models of aging, DS, and AD, and are related to a loss of cholinergic markers and deficits in cognitive function [63,64,89]. The etiology of deficits in proNGF retrograde transport and TrkA expression and signalling in aging, AD, and DS basal forebrain has yet to be confirmed. Emerging literature indicates that oxidative and nitrative stress may be contributing factors. Supporting evidence is discussed in the remainder of this review.

### 3. Oxidative and Nitrative Stress in Neurodegenerative Disease

Highly reactive molecules with unpaired electrons in their outer valence, called free radicals, are a natural by-product of cellular energy metabolism [90]. Free radicals containing oxygen are classified as reactive oxygen species, while those that also contain nitrogen are considered reactive nitrogen species. Reactive oxygen and nitrogen species (ROS/RNS) are commonly produced in mitochondria and are released from microglia during inflammatory responses [90]. ROS/RNS add oxidative and nitrative modifications to cellular components that result in cell damage and death when they are present in high amounts [91]. Under normal conditions, ROS/RNS are quenched by antioxidant systems, preventing them from causing cellular and molecular damage [92].

Oxidative and nitrative stress result when there is an imbalance between ROS/RNS production and ROS/RNS removal by antioxidants [90,92]. In aging and AD, mitochondrial deficits and overactivation of microglia, along with a concurrent decline in antioxidant systems, contribute to the overproduction of ROS/RNS [92–95]. The resulting oxidative and nitrative stress generates extensive cellular and molecular damage in the AD brain [93]. Increased markers of oxidative and nitrative damage, including lipid peroxidation, oxidation of macromolecules, protein carbonyls, and nitrotyrosine residues, are observed in human post-mortem brain tissue from AD patients [95–100]. Elevations in ROS/RNS occur prior to AD pathology in animal models, suggesting that the increases in oxidative and nitrative stress that occur in normal aging are further exacerbated in pathological aging such as AD [101]. Oxidative and nitrative modifications are present within tau neurofibrillary tangles and amyloid-beta plaques [102–104]. Several studies show that ROS stimulate amyloid-beta production and accumulation as well as tau phosphorylation and oligomerization, indicating that oxidative stress contributes to the generation of AD pathology [105]. Amyloid-beta accumulation also generates ROS, indicating that ROS may interact with AD pathology in a positive feedback loop [93].

### 4. ROS/RNS-Induced Deficits in BFCN Viability and Cognitive Function Are Associated with Nitration of proNGF and Reduced TrkA Expression and Signalling

The basal forebrain is especially vulnerable to ROS/RNS [106]. Extensive literature indicates that oxidative and nitrative damage and deficits in antioxidant systems are associated with the cholinergic dysfunction and cognitive decline seen in aging and AD [107–114]. Oxidative stress contributes to BFCN degeneration and the associated cognitive decline,



and antioxidant treatment delays these pathologies [115]. RNS also produces nitration of proNGF in the cortex of aged and cognitively impaired rats [107]. Nitrated proNGF is the main NGF species detected in the AD brain and is correlated with a loss of cholinergic markers and impaired memory performance [107,116]. Nitrated proNGF accumulates in both the human AD cortex and in rodent models of AD [116]. Further investigation is required to elucidate the cause of such accumulation. Potential contributing factors include impaired retrograde transport of proNGF to the basal forebrain and deficits in proNGF maturation. Nitration reduces the ability of mature NGF to activate TrkA and may have a similar effect on proNGF due to the similarity between mature NGF and proNGF in TrkA binding and activation [27,116]. However, this must be tested for proNGF specifically, as proNGF and mature NGF exhibit differences in their TrkA binding affinity and potency of activation of signalling factors [25,27].

ROS/RNS-induced deficits in cognitive and cholinergic functions are also associated with decreased expression of TrkA [117]. Amyloid-beta, which increases oxidative stress in the brain, causes cholinergic dysfunction that is associated with reductions in TrkA expression and memory impairments [106,117]. Antioxidant treatments increase NGF-dependent activation of ERK and CREB and rescue TrkA expression and cognitive and cholinergic functions in rodent models of neurodegenerative disease [117,118]. Together, these findings indicate that the loss of cognitive function induced by oxidative and nitrative stress is associated with disruptions in TrkA expression and signalling.

Several studies indicate that mature NGF is protective against oxidative stress by stimulating antioxidant responses [119,120]. Conversely, deprivation of mature NGF increases ROS, possibly by decreasing mitochondrial function [121]. In PC12 cells, treatment with mature NGF increases cell survival via the PI3K pathway in response to oxidative and nitrative stress [122,123]. In SH-SY5Y cells treated with hydrogen peroxide, antioxidant treatment increases mature NGF protein levels and rescues cell survival via a mechanism dependent on TrkA activation and the activity of the downstream MAPK/ERK signalling pathway, implicating TrkA signalling in defense against oxidative damage [124]. Thus, NGF availability and signalling contribute to cellular protection against oxidative and nitrative insult. However, these effects have yet to be tested specifically for proNGF in the basal forebrain. Nevertheless, overall, these studies highlight the importance of preserving TrkA signalling in the basal forebrain to maintain neuronal protection against oxidative damage and ROS-associated cognitive decline.

## 5. Oxidative and Nitrative Stress Alter the Expression and Signalling of proNGF Receptors

Elevations in ROS may cause an imbalance in TrkA and p75<sup>NTR</sup> receptors in the aging and AD basal forebrain, as several studies indicate that oxidative and nitrative stress alter the expression of these receptors. Similar to what is observed in the aging and AD brain, treatment with ethanol or amyloid-beta, both of which generate oxidative stress, decreases TrkA mRNA and protein expression in the basal forebrain and hippocampus [117,125–127]. TrkA immunoreactivity is also decreased in the basal forebrain of DS mice and in BFCNs aged in vitro, both of which exhibit elevations in ROS [63,115]. Reductions in TrkA mRNA and protein expression in vitro and in vivo can be rescued via antioxidant treatment, indicating a causal role of ROS in TrkA depletion [115,117,124,127,128]. Together, these studies indicate that oxidative stress likely contributes to the decreases in TrkA expression observed in the aging and AD brain.

The reported effects of ROS/RNS on p75<sup>NTR</sup> expression are inconsistent. Oxidative treatment via ethanol or monocrotophos does not affect p75<sup>NTR</sup> protein expression in the rat basal forebrain or in neural stem cells [125,129]. These results are consistent with evidence indicating no differences in p75<sup>NTR</sup> expression in the human AD basal forebrain, aged rodent basal forebrain, or rat BFCNs aged in vitro [63,64,82,83]. However, other studies indicate that the protein levels of p75<sup>NTR</sup> are increased by oxidative and nitrative stress induced by hydrogen peroxide, amyloid-beta, peroxyxynitrite, monocrotophos, and chlorpyrifos in the mouse SN56 basal forebrain cell line, human SH-SY5Y cells and retina,

and rat cortex and hippocampus [128–131]. These results are consistent with other literature indicating an elevation of p75<sup>NTR</sup> in the human AD basal forebrain and entorhinal cortex [86,88]. Differing results may be due to differences in cell types, species, and brain areas studied, as well as variations in treatment conditions used to generate oxidative and nitritative stress.

Maintaining the balance of TrkA and p75<sup>NTR</sup> levels at the axon terminals is critical for regulation of proNGF survival vs. apoptotic signalling [28,29]. ProNGF is neurotrophic in the presence of TrkA but exerts apoptotic effects via p75<sup>NTR</sup> when TrkA is absent [28,29,35]. Therefore, ROS-induced reductions in axonal TrkA expression, with concurrent maintenance or elevation in p75<sup>NTR</sup> expression, are expected to decrease proNGF-TrkA survival signalling while increasing proNGF-p75<sup>NTR</sup> apoptotic signalling. In fact, oxidative and nitritative stress increase the activation of apoptotic signalling factors downstream of p75<sup>NTR</sup>, such as caspase-3, Bax, JNK, and nuclear factor kappa light chain enhancer of activated B cells (NF-κB), in a variety of cell types including neurons, astrocytes, and PC12 cells [123,129,132,133]. Conversely, oxidative stress prevents TrkA phosphorylation and activation of downstream signalling factors such as Akt, ERK1/2, and CREB in neural stem cells, PC12 cells, and astrocytes [129,132,134]. Further, SH-SY5Y cells expressing a presenilin-1 (PS1) mutation causing increased amyloid-beta production, which generates oxidative stress, exhibit impaired NGF-stimulated activation of TrkA and MAPK and mislocalization of TrkA from the membrane to the cytoplasm and nucleus [135]. NGF-induced TrkA phosphorylation and activation of MAPK are also reduced by nitritative stress caused by peroxynitrite in PC12 cells [136]. In the diabetic retina, peroxynitrite decreases TrkA phosphorylation at tyrosine 490 (Y490), the site required for stimulation of the PI3K-Akt survival pathway. This prevents Akt activation, implicating nitritative stress in decreased TrkA signalling and associated reductions in cell viability [130]. Decreased Akt activity is also associated with the TrkA nitration observed in retinal ganglion neurons [130]. TrkA nitration has yet to be assayed in the degenerating basal forebrain. Together, these results highlight that oxidative and nitritative stress decrease TrkA signalling while increasing that of p75<sup>NTR</sup>, leading to neurodegeneration and cell death.

On the other hand, some studies indicate that TrkA signalling is maintained or elevated in response to oxidative and nitritative stress. Nutrient deprivation-induced ROS elevation activates TrkA by decreasing membrane cholesterol in PC12 cells, while hydrogen peroxide and peroxynitrite induce activation of p38 in PC12 cells and diabetic retina [130,137,138]. These findings may be due to differences in reagents used to generate oxidative and nitritative stress as well as differences in the extent and duration of the stress [133]. The effects of ROS/RNS on TrkA and p75<sup>NTR</sup> signalling in the basal forebrain require further investigation.

Although many of these studies use mature NGF to stimulate TrkA and to investigate the relationship between ROS/RNS and downstream signalling, it is likely that these mechanisms are conserved between proNGF and mature NGF. ProNGF is similar to mature NGF in its ability to activate TrkA, induce pro-survival signalling and neurite outgrowth, and be retrogradely transported [25,27–33,61,62]. However, because the two NGF species exhibit minor differences in their affinity for TrkA binding and activation, the effects of oxidative and nitritative stress on proNGF signalling must be tested [27].

## 6. Oxidative and Nitritative Stress Interfere with the Axonal Transport Machinery Required for Retrograde Transport of proNGF

Cytoplasmic dynein is the molecular motor required for the retrograde transport of proNGF and activated Trks [139,140]. The motor domain of dynein, which allows it to interact with and move along the microtubules, is contained within its heavy chain subunit [141]. The dynein heavy chain forms a complex with intermediate and light chains, which regulate cargo binding and heavy chain motor activity [141]. Sequencing studies indicate that dynein intermediate and light chains in flagellar dynein, which have sequence homology to that of cytoplasmic dynein, contain redox-sensitive regions that may be involved in alteration of dynein motor activity [141–143]. These regions contain dithiol

groups that are highly sensitive to oxidative changes. Oxidation of these residues alters dynein ATPase activity, suggesting that oxidative stress may impair dynein-dependent transport by modification of the dithiol-containing regions [141–143]. Interestingly, dynein intermediate and light chains contain the same active site as thioredoxin, an enzyme involved in redox signalling [142,143]. The active site of thioredoxin can be oxidized to repress its activity, providing further evidence that dynein motor function may be inhibited by oxidative stress [144].

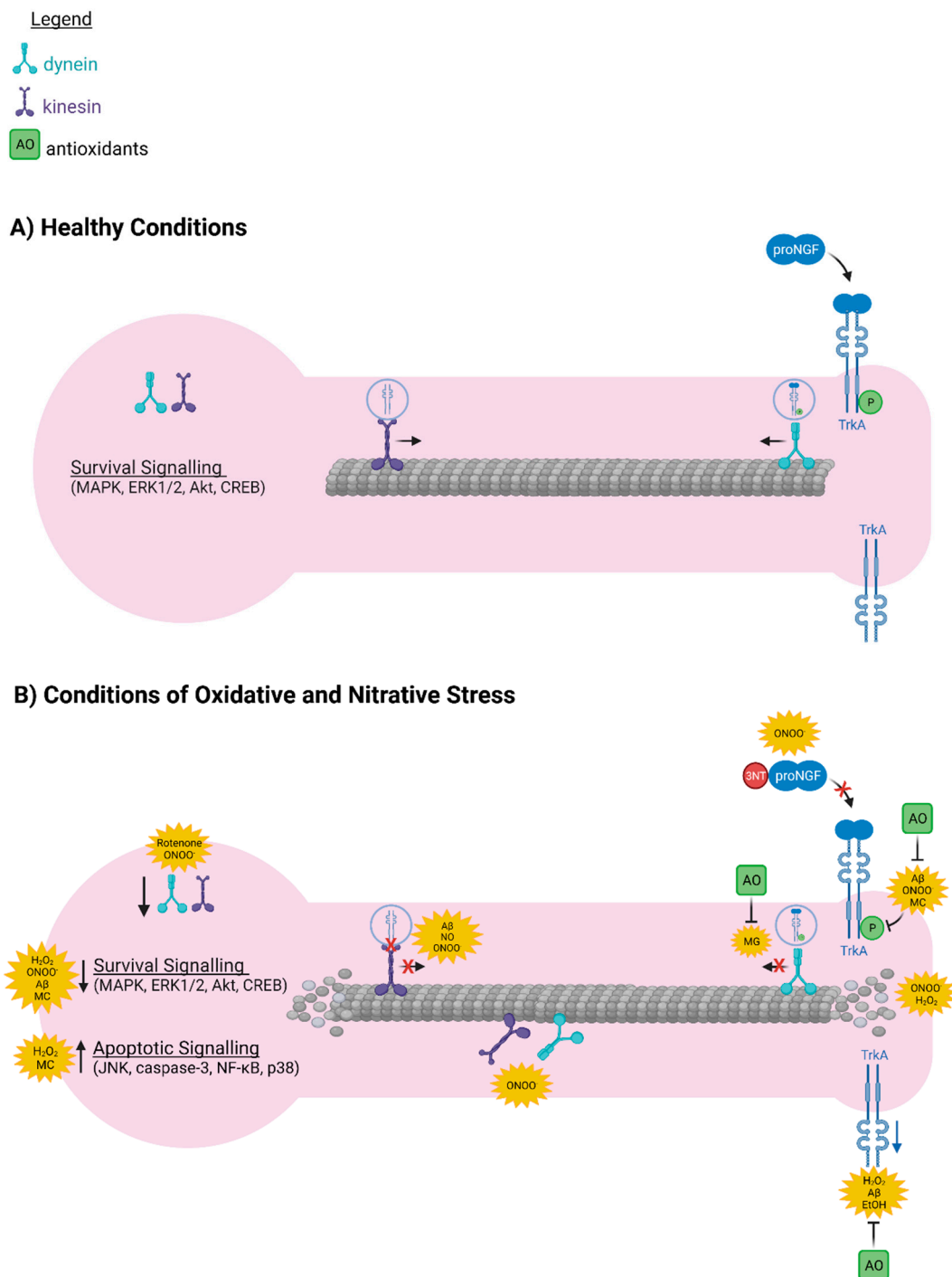
Oxidative and nitrative stress may also affect dynein-dependent axonal transport by altering the expression of key components of the dynein motor [145]. Nitrated tubulin, which is elevated in conditions of nitrative stress, decreases the dynein heavy chain protein and alters its distribution, indicating an impaired association between dynein and microtubules [146]. Similarly, rotenone, a chemical that elevates ROS and generates oxidative damage, decreases the protein expression of dynein heavy chain in cell cultures obtained from the hippocampus, locus coeruleus, and substantia nigra [145,147,148]. Similar decreases are also seen in aged rats following *in vivo* treatment with rotenone [145]. Protein expression of dynactin, a dynein-associated protein, is also decreased in the hippocampus by rotenone treatment [145]. Interestingly, in the locus coeruleus and substantia nigra, dynactin protein levels increase following *in vivo* rotenone treatment, which may be a compensatory response to the reduction in dynein protein levels [145]. The expression of kinesin, the motor protein required for anterograde transport, is also decreased by rotenone, and this decrease is associated with impairments in mitochondrial axonal transport [149].

Another mechanism by which oxidative and nitrative stress may disrupt axonal transport is by decreasing microtubule stability [150]. Peroxynitrite-induced tau nitration decreases the affinity of tau for microtubules and increases its aggregation [150]. Cells containing nitrated tau have altered morphology and neurite retraction, evidence of microtubule destabilization and degradation [150]. Similarly, oxidative stress induced by hydrogen peroxide causes axonal degeneration [151]. Because microtubules are critical for axonal transport, their degeneration caused by oxidative and nitrative stress may cause reductions in retrograde axonal transport [152]. Both tau nitration and microtubule degeneration are observed in the AD brain, suggesting that these pathologies may contribute to deficits in the retrograde transport of proNGF in AD [72,73,150,153].

Nitrative stress decreases axonal transport mediated by KIF1A, the kinesin motor responsible for the anterograde transport of TrkA [154–156]. Anterograde transport of TrkA is required for its expression at the axon terminals and subsequent retrograde transport of TrkA–neurotrophin receptor complexes [139,157]. When anterograde transport of TrkA is impaired by interfering with KIF1A, retrograde transport of TrkA is also disrupted [156]. Furthermore, mutations in presenilin-1 (PS1), which are linked to amyloid-beta accumulation and the generation of oxidative stress, cause the accumulation of TrkA in the cytosol and nucleus rather than expression at the cell surface [135]. These studies highlight that ROS/RNS may disrupt the kinesin-dependent axonal transport of TrkA.

## 7. Conclusions

Oxidative and nitrative stress produce multiple modifications that may impair the retrograde transport and signalling of proNGF by a variety of mechanisms (Figure 2A,B). The resulting reduction in proNGF in the basal forebrain is detrimental to BFCN survival and cognitive function. Which of these mechanisms are most relevant to the basal forebrain and its susceptibility to oxidative insult, neurodegeneration, and the associated cognitive decline in AD is an important area for future investigation.



**Figure 2.** Oxidative and nitritive stress interfere with mechanisms of pro-nerve growth factor (proNGF) axonal transport. **(A)** Under healthy conditions, tropomyosin-related kinase A (TrkA) is expressed at axon terminals. Binding of proNGF induces TrkA autophosphorylation, internalization, and dynein-dependent retrograde transport. These events activate pro-survival signalling factors in the axon and at the cell body to maintain neuronal health. Kinesin motors transport somal TrkA receptors anterogradely to replenish and maintain axonal expression of TrkA. Kinesin and dynein molecular motors are expressed in the neuron and efficiently bind to microtubules to facilitate axonal transport of TrkA. **(B)** In conditions of oxidative and nitritive stress, such as in aging, Down’s syndrome (DS), and Alzheimer’s disease (AD), reactive oxygen and nitrogen species (ROS/RNS) decrease both protein and mRNA expression of TrkA. When nitrated, NGF is less efficient at activating TrkA and its downstream signalling factors, including mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), Akt, extracellular signal-regulated kinase 1/2 (ERK1/2), and cAMP response element-binding protein (CREB). ROS have the opposite effect on activation of signalling factors downstream of the pan-neurotrophin receptor, p75<sup>NTR</sup>, including c-Jun N-terminal kinase (JNK), nuclear factor kappa B (NF-κB), caspase-3, and Bcl-2-associated



X protein (Bax), as all of these are increased in conditions of oxidative and nitrative stress. ROS/RNS decrease protein expression of kinesin and dynein molecular motors and interfere with their interaction with microtubules. ROS/RNS also suppress dynein motor activity and interrupt the interaction between kinesin and its cargo. Finally, ROS/RNS cause axonal degeneration and decrease the affinity of tau for microtubules, leading to microtubule instability and further disruption of axonal transport. Antioxidant treatments are effective in restoring TrkA expression, activation, and retrograde transport. The contributing ROS/RNS generators include amyloid-beta ( $A\beta$ ), hydrogen peroxide ( $H_2O_2$ ), ethanol (EtOH), monocrotophos (MC), methylglyoxal (MG), and peroxynitrite ( $ONOO^-$ ). Diagram was created using BioRender.com. 3NT: 3-nitrotyrosine. Up arrow represents increase, down arrow represents decrease.

Oxidative and nitrative stress decrease TrkA expression while either maintaining or elevating p75<sup>NTR</sup> expression in the basal forebrain. The resulting receptor imbalance is accompanied by decreased survival signalling via TrkA and increased apoptotic signalling via p75<sup>NTR</sup>. Nitration of proNGF, altered function of dynein and kinesin molecular motors, and decreased microtubule stability may also contribute to these deficits. The effects of ROS/RNS-induced deficits in TrkA signalling on cell viability and cognitive function can be rescued with antioxidant treatment. Therapeutic interventions targeting elevations in oxidative and nitrative stress may therefore be beneficial in rescuing the retrograde transport of proNGF in the basal forebrain in aging and AD and subsequently improving BFCN survival and associated cognitive function.

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## References

- Frade, J.M.; Barde, Y.-A. Nerve Growth Factor: Two Receptors, Multiple Functions. *BioEssays* **1998**, *20*, 137–145. [[CrossRef](#)]
- Thoenen, H.; Barde, Y.A. Physiology of Nerve Growth Factor. *Physiol. Rev.* **1980**, *60*, 1284–1335. [[CrossRef](#)] [[PubMed](#)]
- Kaplan, D.R.; Martin-Zanca, D.; Parada, L.F. Tyrosine Phosphorylation and Tyrosine Kinase Activity of the Trk Proto-Oncogene Product Induced by NGF. *Nature* **1991**, *350*, 158–160. [[CrossRef](#)] [[PubMed](#)]
- Klesse, L.J.; Meyers, K.A.; Marshall, C.J.; Parada, L.F. Nerve Growth Factor Induces Survival and Differentiation through Two Distinct Signaling Cascades in PC12 Cells. *Oncogene* **1999**, *18*, 2055–2068. [[CrossRef](#)]
- Kim, U.H.; Fink, D.; Kim, H.S.; Park, D.J.; Contreras, M.L.; Guroff, G.; Rhee, S.G. Nerve Growth Factor Stimulates Phosphorylation of Phospholipase C-Gamma in PC12 Cells. *J. Biol. Chem.* **1991**, *266*, 1359–1362. [[CrossRef](#)]
- Vetter, M.L.; Martin-Zanca, D.; Parada, L.F.; Bishop, J.M.; Kaplan, D.R. Nerve Growth Factor Rapidly Stimulates Tyrosine Phosphorylation of Phospholipase C-Gamma 1 by a Kinase Activity Associated with the Product of the Trk Protooncogene. *Proc. Nat. Acad. Sci. USA* **1991**, *88*, 5650–5654. [[CrossRef](#)]
- Kaplan, D.R.; Miller, F.D. Neurotrophin Signal Transduction in the Nervous System. *Curr. Opin. Neurobiol.* **2000**, *10*, 381–391. [[CrossRef](#)]
- Stephens, R.M.; Loeb, D.M.; Copeland, T.D.; Pawson, T.; Greene, L.A.; Kaplan, D.R. Trk Receptors Use Redundant Signal Transduction Pathways Involving SHC and PLC- $\Gamma$ 1 to Mediate NGF Responses. *Neuron* **1994**, *12*, 691–705. [[CrossRef](#)]
- Obermeier, A.; Bradshaw, R.A.; Seedorf, K.; Choidas, A.; Schlessinger, J.; Ullrich, A. Neuronal Differentiation Signals Are Controlled by Nerve Growth Factor Receptor/Trk Binding Sites for SHC and PLC Gamma. *EMBO J.* **1994**, *13*, 1585–1590. [[CrossRef](#)]
- Xing, J.; Kornhauser, J.M.; Xia, Z.; Thiele, E.A.; Greenberg, M.E. Nerve Growth Factor Activates Extracellular Signal-Regulated Kinase and P38 Mitogen-Activated Protein Kinase Pathways to Stimulate CREB Serine 133 Phosphorylation. *Mol. Cell. Biol.* **1998**, *18*, 1946–1955. [[CrossRef](#)]
- Saura, C.A.; Valero, J. The Role of CREB Signaling in Alzheimer’s Disease and Other Cognitive Disorders. *Rev. Neurosci.* **2011**, *22*, 153–169. [[CrossRef](#)] [[PubMed](#)]
- Roux, P.P.; Barker, P.A. Neurotrophin Signaling through the P75 Neurotrophin Receptor. *Prog. Neurobiol.* **2002**, *67*, 203–233. [[CrossRef](#)]
- Mahadeo, D.; Kaplan, L.; Chao, M.V.; Hempstead, B.L. High Affinity Nerve Growth Factor Binding Displays a Faster Rate of Association than P140trk Binding. Implications for Multi-Subunit Polypeptide Receptors. *J. Biol. Chem.* **1994**, *269*, 6884–6891. [[CrossRef](#)]

14. Selby, M.J.; Edwards, R.; Sharp, F.; Rutter, W.J. Mouse Nerve Growth Factor Gene: Structure and Expression. *Mol. Cell. Biol.* **1987**, *7*, 3057–3064. [[CrossRef](#)]
15. Racke, M.M.; Mason, P.J.; Johnson, M.P.; Brankamp, R.G.; Linnik, M.D. Demonstration of a Second Pharmacologically Active Promoter Region in the NGF Gene That Induces Transcription at Exon 3. *Mol. Brain Res.* **1996**, *41*, 192–199. [[CrossRef](#)]
16. Darling, T.L.J.; Petrides, P.E.; Beguin, P.; Frey, P.; Shooter, E.M.; Selby, M.; Rutter, W.J. The Biosynthesis and Processing of Proteins in the Mouse 7S Nerve Growth Factor Complex. *Cold Spring Harb. Symp. Quant. Biol.* **1983**, *48*, 427–434. [[CrossRef](#)]
17. Ullrich, A.; Gray, A.; Berman, C.; Dull, T.J. Human  $\beta$ -Nerve Growth Factor Gene Sequence Highly Homologous to That of Mouse. *Nature* **1983**, *303*, 821–825. [[CrossRef](#)]
18. Edwards, R.H.; Selby, M.J.; Rutter, W.J. Differential RNA Splicing Predicts Two Distinct Nerve Growth Factor Precursors. *Nature* **1986**, *319*, 784–787. [[CrossRef](#)]
19. Edwards, R.H.; Selby, M.J.; Mobley, W.C.; Weinrich, S.L.; Hruby, D.E.; Rutter, W.J. Processing and Secretion of Nerve Growth Factor: Expression in Mammalian Cells with a Vaccinia Virus Vector. *Mol. Cell. Biol.* **1988**, *8*, 2456–2464. [[CrossRef](#)] [[PubMed](#)]
20. Fahnstock, M. Structure and Biosynthesis of Nerve Growth Factor. *Curr. Top. Microbiol. Immunol.* **1991**, *165*, 1–26. [[CrossRef](#)] [[PubMed](#)]
21. Lee, R. Regulation of Cell Survival by Secreted Proneurotrophins. *Science* **2001**, *294*, 1945–1948. [[CrossRef](#)] [[PubMed](#)]
22. Seidah, N.G.; Benjannet, S.; Pareek, S.; Savaria, D.; Hamelin, J.; Goulet, B.; Laliberté, J.; Lazure, C.; Chrétien, M.; Murphy, R.A. Cellular Processing of the Nerve Growth Factor Precursor by the Mammalian Pro-Protein Convertases. *Biochem. J.* **1996**, *314*, 951–960. [[CrossRef](#)]
23. Bruno, M.A.; Cuello, A.C. Activity-Dependent Release of Precursor Nerve Growth Factor, Conversion to Mature Nerve Growth Factor, and Its Degradation by a Protease Cascade. *Proc. Nat. Acad. Sci. USA* **2006**, *103*, 6735–6740. [[CrossRef](#)] [[PubMed](#)]
24. Fahnstock, M.; Michalski, B.; Xu, B.; Coughlin, M. The Precursor Pro-Nerve Growth Factor Is the Predominant Form of Nerve Growth Factor in Brain and Is Increased in Alzheimer’s Disease. *Mol. Cell. Neurosci.* **2001**. [[CrossRef](#)] [[PubMed](#)]
25. Fahnstock, M.; Yu, G.; Michalski, B.; Mathew, S.; Colquhoun, A.; Ross, G.M.; Coughlin, M.D. The Nerve Growth Factor Precursor ProNGF Exhibits Neurotrophic Activity but Is Less Active than Mature Nerve Growth Factor. *J. Neurochem.* **2004**, *89*, 581–592. [[CrossRef](#)] [[PubMed](#)]
26. Fahnstock, M.; Yu, G.; Coughlin, M.D. ProNGF: A neurotrophic or an apoptotic molecule? In *Progress in Brain Research. NGF and Related Molecules in Health and Disease*; Elsevier: Amsterdam, The Netherlands, 2004; Volume 146, pp. 101–110.
27. Clewes, O.; Fahey, M.S.; Tyler, S.J.; Watson, J.J.; Seok, H.; Catania, C.; Cho, K.; Dawbarn, D.; Allen, S.J. Human ProNGF: Biological Effects and Binding Profiles at TrkA, P75NTR and Sortilin. *J. Neurochem.* **2008**, *107*, 1124–1135. [[CrossRef](#)]
28. Masoudi, R.; Ioannou, M.S.; Coughlin, M.D.; Pagadala, P.; Neet, K.E.; Clewes, O.; Allen, S.J.; Dawbarn, D.; Fahnstock, M. Biological Activity of Nerve Growth Factor Precursor Is Dependent upon Relative Levels of Its Receptors. *J. Biol. Chem.* **2009**, *284*, 18424–18433. [[CrossRef](#)] [[PubMed](#)]
29. Ioannou, M.S.; Fahnstock, M. ProNGF, but Not NGF, Switches from Neurotrophic to Apoptotic Activity in Response to Reductions in TrkA Receptor Levels. *Int. J. Mol. Sci.* **2017**, *18*, 599. [[CrossRef](#)]
30. Rattenholl, A.; Lilie, H.; Grossmann, A.; Stern, A.; Schwarz, E.; Rudolph, R. The Pro-Sequence Facilitates Folding of Human Nerve Growth Factor from Escherichia Coli Inclusion Bodies. *Eur. J. Biochem.* **2001**, *268*, 3296–3303. [[CrossRef](#)]
31. Buttigieg, H.; Kawaja, M.D.; Fahnstock, M. Neurotrophic Activity of ProNGF in Vivo. *Exp. Neurol.* **2007**, *204*, 832–835. [[CrossRef](#)]
32. Saboori, A.M.; Young, M. Nerve Growth Factor: Biosynthetic Products of the Mouse Salivary Glands. Characterization of Stable High Molecular Weight and 32,000-Dalton Nerve Growth Factors. *Biochemistry* **1986**, *25*, 5565–5571. [[CrossRef](#)] [[PubMed](#)]
33. Chen, Y.; Dicou, E.; Djakiew, D. Characterization of Nerve Growth Factor Precursor Protein Expression in Rat Round Spermatids and the Trophic Effects of Nerve Growth Factor in the Maintenance of Sertoli Cell Viability. *Mol. Cell. Endocrinol.* **1997**, *127*, 129–136. [[CrossRef](#)]
34. Nykjaer, A.; Lee, R.; Teng, K.K.; Jansen, P.; Madsen, P.; Nielsen, M.S.; Jacobsen, C.; Kliemann, M.; Schwarz, E.; Willnow, T.E.; et al. Sortilin Is Essential for ProNGF-Induced Neuronal Cell Death. *Nature* **2004**, *427*, 843–848. [[CrossRef](#)] [[PubMed](#)]
35. Fahnstock, M.; Shekari, A. ProNGF and Neurodegeneration in Alzheimer’s Disease. *Front. Neurosci.* **2019**, *13*. [[CrossRef](#)]
36. Knopman, D.S.; Amieva, H.; Petersen, R.C.; Chételat, G.; Holtzman, D.M.; Hyman, B.T.; Nixon, R.A.; Jones, D.T. Alzheimer Disease. *Nat. Rev. Dis. Primers* **2021**, *7*, 33. [[CrossRef](#)]
37. Schmitz, T.W.; Nathan Spreng, R. Basal Forebrain Degeneration Precedes and Predicts the Cortical Spread of Alzheimer’s Pathology. *Nat. Commun.* **2016**, *7*, 13249. [[CrossRef](#)] [[PubMed](#)]
38. Colom, L.V. Septal Networks: Relevance to Theta Rhythm, Epilepsy and Alzheimer’s Disease. *J. Neurochem.* **2006**, *96*, 609–623. [[CrossRef](#)]
39. Ferreira-Vieira, T.H.; Guimaraes, I.M.; Silva, F.R.; Ribeiro, F.M. Alzheimer’s Disease: Targeting the Cholinergic System. *Curr. Neuropharmacol.* **2016**, *14*, 101–115. [[CrossRef](#)]
40. Ypsilanti, A.R.; Girão da Cruz, M.T.; Burgess, A.; Aubert, I. The Length of Hippocampal Cholinergic Fibers Is Reduced in the Aging Brain. *Neurobiol. Aging* **2008**, *29*, 1666–1679. [[CrossRef](#)]
41. Baxter, M.G.; Chiba, A.A. Cognitive Functions of the Basal Forebrain. *Curr. Opin. Neurobiol.* **1999**, *9*, 178–183. [[CrossRef](#)]
42. Sarter, M.; Parikh, V. Choline Transporters, Cholinergic Transmission and Cognition. *Nat. Rev. Neurosci.* **2005**, *6*, 48–56. [[CrossRef](#)] [[PubMed](#)]

43. Mann, D.M.; Yates, P.O.; Marcyniuk, B.; Ravindra, C.R. Pathological Evidence for Neurotransmitter Deficits in Down's Syndrome of Middle Age. *J. Ment. Defic. Res.* **1985**, *29*, 125–135. [[CrossRef](#)]
44. Wisniewski, K.E.; Dalton, A.J.; McLachlan, D.R.C.; Wen, G.Y.; Wisniewski, H.M. Alzheimer's Disease in Down's Syndrome: Clinicopathologic Studies. *Neurology* **1985**, *35*, 957. [[CrossRef](#)] [[PubMed](#)]
45. Hartikka, J.; Hefti, F. Development of Septal Cholinergic Neurons in Culture: Plating Density and Glial Cells Modulate Effects of NGF on Survival, Fiber Growth, and Expression of Transmitter-Specific Enzymes. *J. Neurosci.* **1988**, *8*, 2967–2985. [[CrossRef](#)] [[PubMed](#)]
46. Hatanaka, H.; Tsukui, H.; Nihonmatsu, I. Developmental Change in the Nerve Growth Factor Action from Induction of Choline Acetyltransferase to Promotion of Cell Survival in Cultured Basal Forebrain Cholinergic Neurons from Postnatal Rats. *Dev. Brain Res.* **1988**, *39*, 85–95. [[CrossRef](#)]
47. Friedman, W.J.; Ibáñez, C.F.; Hallböök, F.; Persson, H.; Cain, L.D.; Dreyfus, C.F.; Black, I.B. Differential Actions of Neurotrophins in the Locus Coeruleus and Basal Forebrain. *Exp. Neurol.* **1993**, *119*, 72–78. [[CrossRef](#)] [[PubMed](#)]
48. Hefti, F. Nerve Growth Factor Promotes Survival of Septal Cholinergic Neurons after Fimbrial Transections. *J. Neurosci.* **1986**, *6*, 2155–2162. [[CrossRef](#)]
49. Lapchak, P.A.; Hefti, F. Effect of Recombinant Human Nerve Growth Factor on Presynaptic Cholinergic Function in Rat Hippocampal Slices Following Partial Septohippocampal Lesions: Measures of [3H]Acetylcholine Synthesis, [3H]Acetylcholine Release and Choline Acetyltransferase Activity. *Neuroscience* **1991**, *42*, 639–649. [[CrossRef](#)]
50. Koliatsos, V.E.; Price, D.L.; Gouras, G.K.; Cayouette, M.H.; Burton, L.E.; Winslow, J.W. Highly Selective Effects of Nerve Growth Factor, Brain-Derived Neurotrophic Factor, and Neurotrophin-3 on Intact and Injured Basal Forebrain Magnocellular Neurons. *J. Comp. Neurol.* **1994**, *343*, 247–262. [[CrossRef](#)]
51. Williams, L.R.; Varon, S.; Peterson, G.M.; Wictorin, K.; Fischer, W.; Bjorklund, A.; Gage, F.H. Continuous Infusion of Nerve Growth Factor Prevents Basal Forebrain Neuronal Death after Fimbria Fornix Transection. *Proc. Nat. Acad. Sci. USA* **1986**, *83*, 9231–9235. [[CrossRef](#)]
52. Lauterborn, J.C.; Isackson, P.J.; Gall, C.M. Nerve Growth Factor mRNA-Containing Cells Are Distributed within Regions of Cholinergic Neurons in the Rat Basal Forebrain. *J. Comp. Neurol.* **1991**, *306*, 439–446. [[CrossRef](#)]
53. Korsching, S.; Auburger, G.; Heumann, R.; Scott, J.; Thoenen, H. Levels of Nerve Growth Factor and Its mRNA in the Central Nervous System of the Rat Correlate with Cholinergic Innervation. *EMBO J.* **1985**, *4*, 1389–1393. [[CrossRef](#)]
54. Lauterborn, J.C.; Bizon, J.L.; Tran, T.M.; Gall, C.M. NGF mRNA Is Expressed by GABAergic but Not Cholinergic Neurons in Rat Basal Forebrain. *J. Comp. Neurol.* **1995**, *360*, 454–462. [[CrossRef](#)] [[PubMed](#)]
55. Francis-Turner, L.; Valoušková, V. Nerve Growth Factor and Nootropic Drug Cerebrolysin but Not Fibroblast Growth Factor Can Reduce Spatial Memory Impairment Elicited by Fimbria-Fornix Transection: Short-Term Study. *Neurosci. Lett.* **1996**, *202*, 193–196. [[CrossRef](#)]
56. Seiler, M.; Schwab, M.E. Specific Retrograde Transport of Nerve Growth Factor (NGF) from Neocortex to Nucleus Basalis in the Rat. *Brain Res.* **1984**, *300*, 33–39. [[CrossRef](#)]
57. Barford, K.; Deppmann, C.; Winckler, B. The Neurotrophin Receptor Signaling Endosome: Where Trafficking Meets Signaling. *Dev. Neurobiol.* **2017**, *77*, 405–418. [[CrossRef](#)] [[PubMed](#)]
58. Delcroix, J.-D.; Valletta, J.S.; Wu, C.; Hunt, S.J.; Kowal, A.S.; Mobley, W.C. NGF Signaling in Sensory Neurons: Evidence That Early Endosomes Carry NGF Retrograde Signals. *Neuron* **2003**, *39*, 69–84. [[CrossRef](#)]
59. Salehi, A.; Delcroix, J.-D.; Belichenko, P.V.; Zhan, K.; Wu, C.; Valletta, J.S.; Takimoto-Kimura, R.; Kleschevnikov, A.M.; Sambamurti, K.; Chung, P.P.; et al. Increased App Expression in a Mouse Model of Down's Syndrome Disrupts NGF Transport and Causes Cholinergic Neuron Degeneration. *Neuron* **2006**, *51*, 29–42. [[CrossRef](#)]
60. Cosker, K.E.; Pazyra-Murphy, M.F.; Fenstermacher, S.J.; Segal, R.A. Target-Derived Neurotrophins Coordinate Transcription and Transport of Bclw to Prevent Axonal Degeneration. *J. Neurosci.* **2013**, *33*, 5195–5207. [[CrossRef](#)]
61. Di Matteo, P.; Calvello, M.; Luin, S.; Marchetti, L.; Cattaneo, A. An Optimized Procedure for the Site-Directed Labeling of NGF and ProNGF for Imaging Purposes. *Front. Mol. Biosci.* **2017**, *4*. [[CrossRef](#)]
62. De Nadai, T.; Marchetti, L.; Di Rienzo, C.; Calvello, M.; Signore, G.; Di Matteo, P.; Gobbo, F.; Turturro, S.; Meucci, S.; Viegi, A.; et al. Precursor and Mature NGF Live Tracking: One versus Many at a Time in the Axons. *Sci. Rep.* **2016**, *6*, 20272. [[CrossRef](#)]
63. Shekari, A.; Fahnstock, M. Retrograde Axonal Transport of BDNF and ProNGF Diminishes with Age in Basal Forebrain Cholinergic Neurons. *Neurobiol. Aging* **2019**, *84*, 131–140. [[CrossRef](#)]
64. Cooper, J.D.; Lindholm, D.; Sofroniew, M.V. Reduced Transport of [125I]Nerve Growth Factor by Cholinergic Neurons and down-Regulated Trka Expression in the Medial Septum of Aged Rats. *Neuroscience* **1994**, *62*, 625–629. [[CrossRef](#)]
65. Bearer, E.L.; Manifold-Wheeler, B.C.; Medina, C.S.; Gonzales, A.G.; Chaves, F.L.; Jacobs, R.E. Alterations of Functional Circuitry in Aging Brain and the Impact of Mutated APP Expression. *Neurobiol. Aging* **2018**, *70*, 276–290. [[CrossRef](#)]
66. Niewiadomska, G.; Baksalerska-Pazera, M. Age-Dependent Changes in Axonal Transport and Cellular Distribution of Tau 1 in the Rat Basal Forebrain Neurons. *NeuroReport* **2003**, *14*, 1701–1706. [[CrossRef](#)] [[PubMed](#)]
67. Narisawa-Saito, M.; Wakabayashi, K.; Tsuji, S.; Takahashi, H.; Nawa, H. Regional Specificity of Alterations in NGF, BDNF, and NT-3 Levels in Alzheimer's Disease. *NeuroReport* **1996**, *7*, 2925–2928. [[CrossRef](#)] [[PubMed](#)]
68. Crutcher, K.A.; Scott, S.A.; Liang, S.; Everson, W.V.; Weingartner, J. Detection of NGF-like Activity in Human Brain Tissue: Increased Levels in Alzheimer's Disease. *J. Neurosci.* **1993**, *13*, 2540–2550. [[CrossRef](#)]



69. Fahnstock, M.; Scott, S.A.; Jetté, N.; Weingartner, J.A.; Crutcher, K.A. Nerve Growth Factor mRNA and Protein Levels Measured in the Same Tissue from Normal and Alzheimer's Disease Parietal Cortex. *Mol. Brain Res.* **1996**, *42*, 175–178. [[CrossRef](#)]
70. Scott, S.A.; Mufson, E.J.; Weingartner, J.A.; Skau, K.A.; Crutcher, K.A. Nerve Growth Factor in Alzheimer's Disease: Increased Levels throughout the Brain Coupled with Declines in Nucleus Basalis. *J. Neurosci.* **1995**, *15*, 6213–6221. [[CrossRef](#)]
71. Mufson, E.J.; Conner, J.M.; Kordower, J.H. Nerve Growth Factor in Alzheimer's Disease: Defective Retrograde Transport to Nucleus Basalis. *NeuroReport* **1995**, *6*, 1063–1066. [[CrossRef](#)] [[PubMed](#)]
72. Peng, S.; Wu, J.; Mufson, E.J.; Fahnstock, M. Increased ProNGF Levels in Subjects with Mild Cognitive Impairment and Mild Alzheimer Disease. *J. Neuropathol. Exp. Neurol.* **2004**, *63*, 641–649. [[CrossRef](#)]
73. Perez, S.E.; He, B.; Muhammad, N.; Oh, K.-J.; Fahnstock, M.; Ikonovic, M.D.; Mufson, E.J. Cholinergic Basal Forebrain System Alterations in 3xTg-AD Transgenic Mice. *Neurobiol. Dis.* **2011**, *41*, 338–352. [[CrossRef](#)]
74. Iulita, M.F.; Bistué Millón, M.B.; Pentz, R.; Aguilar, L.F.; Do Carmo, S.; Allard, S.; Michalski, B.; Wilson, E.N.; Ducatenzeiler, A.; Bruno, M.A.; et al. Differential Deregulation of NGF and BDNF Neurotrophins in a Transgenic Rat Model of Alzheimer's Disease. *Neurobiol. Dis.* **2017**, *108*, 307–323. [[CrossRef](#)]
75. Iulita, M.F.; Do Carmo, S.; Ower, A.K.; Fortress, A.M.; Aguilar, L.F.; Hanna, M.; Wisniewski, T.; Granholm, A.-C.; Buhusi, M.; Busciglio, J.; et al. Nerve Growth Factor Metabolic Dysfunction in Down's Syndrome Brains. *Brain* **2014**, *137*, 860–872. [[CrossRef](#)]
76. Pentz, R.; Iulita, M.F.; Ducatenzeiler, A.; Bennett, D.A.; Cuello, A.C. The Human Brain NGF Metabolic Pathway Is Impaired in the Pre-Clinical and Clinical Continuum of Alzheimers Disease. *Mol. Psychiatry* **2020**, 1–15. [[CrossRef](#)] [[PubMed](#)]
77. Pentz, R.; Iulita, M.F.; Mikutra-Cencora, M.; Ducatenzeiler, A.; Bennett, D.A.; Cuello, A.C. A New Role for Matrix Metalloproteinase-3 in the NGF Metabolic Pathway: Proteolysis of Mature NGF and Sex-Specific Differences in the Continuum of Alzheimer's Pathology. *Neurobiol. Dis.* **2021**, *148*, 105150. [[CrossRef](#)] [[PubMed](#)]
78. Jetté, N.; Cole, M.S.; Fahnstock, M. NGF mRNA Is Not Decreased in Frontal Cortex from Alzheimer's Disease Patients. *Mol. Brain Res.* **1994**, *25*, 242–250. [[CrossRef](#)]
79. Goedert, M.; Fine, A.; Hunt, S.P.; Ullrich, A. Nerve Growth Factor mRNA in Peripheral and Central Rat Tissues and in the Human Central Nervous System: Lesion Effects in the Rat Brain and Levels in Alzheimer's Disease. *Mol. Brain Res.* **1986**, *1*, 85–92. [[CrossRef](#)]
80. Allard, S.; Leon, W.C.; Pakavathkumar, P.; Bruno, M.A.; Ribeiro-da-Silva, A.; Cuello, A.C. Impact of the NGF Maturation and Degradation Pathway on the Cortical Cholinergic System Phenotype. *J. Neurosci.* **2012**, *32*, 2002–2012. [[CrossRef](#)]
81. Allard, S.; Jacobs, M.L.; Do Carmo, S.; Cuello, A.C. Compromise of Cortical ProNGF Maturation Causes Selective Retrograde Atrophy in Cholinergic Nucleus Basalis Neurons. *Neurobiol. Aging* **2018**, *67*, 10–20. [[CrossRef](#)]
82. Hock, C.; Heese, K.; Müller-Spahn, F.; Hulette, C.; Rosenberg, C.; Otten, U. Decreased TrkA Neurotrophin Receptor Expression in the Parietal Cortex of Patients with Alzheimer's Disease. *Neurosci. Lett.* **1998**, *241*, 151–154. [[CrossRef](#)]
83. Mufson, E.J.; Li, J.M.; Sobreviela, T.; Kordower, J.H. Decreased TrkA Gene Expression within Basal Forebrain Neurons in Alzheimer's Disease. *NeuroReport* **1996**, *8*, 25–29. [[CrossRef](#)]
84. Mufson, E.J.; Lavine, N.; Jaffar, S.; Kordower, J.H.; Quirion, R.; Saragovi, H.U. Reduction in P140-TrkA Receptor Protein within the Nucleus Basalis and Cortex in Alzheimer's Disease. *Exp. Neurol.* **1997**, *146*, 91–103. [[CrossRef](#)]
85. Salehi, A.; Verhaagen, J.; Dijkhuizen, P.A.; Swaab, D.F. Co-Localization of High-Affinity Neurotrophin Receptors in Nucleus Basalis of Meynert Neurons and Their Differential Reduction in Alzheimer's Disease. *Neuroscience* **1996**, *75*, 373–387. [[CrossRef](#)]
86. Podlesniy, P.; Kichev, A.; Pedraza, C.; Saurat, J.; Encinas, M.; Perez, B.; Ferrer, I.; Espinet, C. Pro-NGF from Alzheimer's Disease and Normal Human Brain Displays Distinctive Abilities to Induce Processing and Nuclear Translocation of Intracellular Domain of P75NTR and Apoptosis. *Am. J. Pathol.* **2006**, *169*, 119–131. [[CrossRef](#)] [[PubMed](#)]
87. Lee, H.-K.; Kumar, P.; Fu, Q.; Rosen, K.M.; Querfurth, H.W. The Insulin/Akt Signaling Pathway Is Targeted by Intracellular  $\beta$ -Amyloid. *Mol. Biol. Cell* **2009**, *20*, 1533–1544. [[CrossRef](#)] [[PubMed](#)]
88. Ernfors, P.; Lindfors, N.; Chan-Palay, V.; Persson, H. Cholinergic Neurons of the Nucleus Basalis Express Elevated Levels of Nerve Growth Factor Receptor mRNA in Senile Dementia of the Alzheimer Type. *Dement. Geriatr. Cogn. Disord.* **1990**, *1*, 138–145. [[CrossRef](#)]
89. Granholm, A.-C.E.; Sanders, L.A.; Crnic, L.S. Loss of Cholinergic Phenotype in Basal Forebrain Coincides with Cognitive Decline in a Mouse Model of Down's Syndrome. *Exp. Neurol.* **2000**, *161*, 647–663. [[CrossRef](#)]
90. Ozcan, A.; Ogun, M. *Biochemistry of Reactive Oxygen and Nitrogen Species*; IntechOpen: London, UK, 2015; ISBN 978-953-51-2200-5.
91. Cobb, C.A.; Cole, M.P. Oxidative and Nitrate Stress in Neurodegeneration. *Neurobiol. Dis.* **2015**, *84*, 4–21. [[CrossRef](#)]
92. Kim, G.H.; Kim, J.E.; Rhie, S.J.; Yoon, S. The Role of Oxidative Stress in Neurodegenerative Diseases. *Exp. Neurobiol.* **2015**, *24*, 325–340. [[CrossRef](#)]
93. Markesbery, W.R. Oxidative Stress Hypothesis in Alzheimer's Disease. *Free Radic. Biol. Med.* **1997**, *23*, 134–147. [[CrossRef](#)]
94. Kim, T.-S.; Pae, C.-U.; Yoon, S.-J.; Jang, W.-Y.; Lee, N.J.; Kim, J.-J.; Lee, S.-J.; Lee, C.; Paik, I.-H.; Lee, C.-U. Decreased Plasma Antioxidants in Patients with Alzheimer's Disease. *Int. J. Geriatr. Psychiatry* **2006**, *21*, 344–348. [[CrossRef](#)]
95. Hensley, K.; Maidt, M.L.; Yu, Z.; Sang, H.; Markesbery, W.R.; Floyd, R.A. Electrochemical Analysis of Protein Nitrotyrosine and Dityrosine in the Alzheimer Brain Indicates Region-Specific Accumulation. *J. Neurosci.* **1998**, *18*, 8126–8132. [[CrossRef](#)]
96. Mecocci, P.; Beal, M.F.; Cecchetti, R.; Polidori, M.C.; Cherubini, A.; Chionne, F.; Avellini, L.; Romano, G.; Senin, U. Mitochondrial Membrane Fluidity and Oxidative Damage to Mitochondrial DNA in Aged and AD Human Brain. *Mol. Chem. Neuropathol.* **1997**, *31*, 53–64. [[CrossRef](#)] [[PubMed](#)]

97. Lyras, L.; Cairns, N.J.; Jenner, A.; Jenner, P.; Halliwell, B. An Assessment of Oxidative Damage to Proteins, Lipids, and DNA in Brain from Patients with Alzheimer's Disease. *J. Neurochem.* **1997**, *68*, 2061–2069. [[CrossRef](#)] [[PubMed](#)]
98. Lovell, M.A.; Ehmann, W.D.; Butler, S.M.; Markesbery, W.R. Elevated Thiobarbituric Acid-Reactive Substances and Antioxidant Enzyme Activity in the Brain in Alzheimer's Disease. *Neurology* **1995**, *45*, 1594–1601. [[CrossRef](#)] [[PubMed](#)]
99. Subbarao, K.V.; Richardson, J.S.; Ang, L.C. Autopsy Samples of Alzheimer's Cortex Show Increased Peroxidation In Vitro. *J. Neurochem.* **1990**, *55*, 342–345. [[CrossRef](#)] [[PubMed](#)]
100. Smith, C.D.; Carney, J.M.; Starke-Reed, P.E.; Oliver, C.N.; Stadtman, E.R.; Floyd, R.A.; Markesbery, W.R. Excess Brain Protein Oxidation and Enzyme Dysfunction in Normal Aging and in Alzheimer Disease. *Proc. Nat. Acad. Sci. USA* **1991**, *88*, 10540–10543. [[CrossRef](#)] [[PubMed](#)]
101. Praticò, D.; Uryu, K.; Leight, S.; Trojanowski, J.Q.; Lee, V.M.-Y. Increased Lipid Peroxidation Precedes Amyloid Plaque Formation in an Animal Model of Alzheimer Amyloidosis. *J. Neurosci.* **2001**, *21*, 4183–4187. [[CrossRef](#)]
102. Yan, S.D.; Chen, X.; Schmidt, A.M.; Brett, J.; Godman, G.; Zou, Y.S.; Scott, C.W.; Caputo, C.; Frappier, T.; Smith, M.A. Glycated Tau Protein in Alzheimer Disease: A Mechanism for Induction of Oxidant Stress. *Proc. Nat. Acad. Sci. USA* **1994**, *91*, 7787–7791. [[CrossRef](#)]
103. Good, P.F.; Werner, P.; Hsu, A.; Olanow, C.W.; Perl, D.P. Evidence of Neuronal Oxidative Damage in Alzheimer's Disease. *Am. J. Pathol.* **1996**, *149*, 21–28.
104. Smith, M.A.; Taneda, S.; Richey, P.L.; Miyata, S.; Yan, S.D.; Stern, D.; Sayre, L.M.; Monnier, V.M.; Perry, G. Advanced Maillard Reaction End Products Are Associated with Alzheimer Disease Pathology. *Proc. Nat. Acad. Sci. USA* **1994**, *91*, 5710–5714. [[CrossRef](#)] [[PubMed](#)]
105. Zhao, Y.; Zhao, B. Oxidative Stress and the Pathogenesis of Alzheimer's Disease. *Oxid. Med. Cell. Longev.* **2013**, *2013*, 316523. [[CrossRef](#)]
106. Mattson, M.P.; Pedersen, W.A. Effects of Amyloid Precursor Protein Derivatives and Oxidative Stress on Basal Forebrain Cholinergic Systems in Alzheimer's Disease. *Int. J. Dev. Neurosci.* **1998**, *16*, 737–753. [[CrossRef](#)]
107. Bruno, M.A.; Cuello, A.C. Cortical Peroxynitration of Nerve Growth Factor in Aged and Cognitively Impaired Rats. *Neurobiol. Aging* **2012**, *33*, 1927–1937. [[CrossRef](#)] [[PubMed](#)]
108. Berr, C. Cognitive Impairment and Oxidative Stress in the Elderly: Results of Epidemiological Studies. *BioFactors* **2000**, *13*, 205–209. [[CrossRef](#)] [[PubMed](#)]
109. Perkins, A.J.; Hendrie, H.C.; Callahan, C.M.; Gao, S.; Unverzagt, F.W.; Xu, Y.; Hall, K.S.; Hui, S.L. Association of Antioxidants with Memory in a Multiethnic Elderly Sample Using the Third National Health and Nutrition Examination Survey. *Am. J. Epidemiol.* **1999**, *150*, 37–44. [[CrossRef](#)]
110. Perrig, W.J.; Perrig, P.; Stähelin, H.B. The Relation between Antioxidants and Memory Performance in the Old and Very Old. *J. Am. Geriatr. Soc.* **1997**, *45*, 718–724. [[CrossRef](#)]
111. Rinaldi, P.; Polidori, M.C.; Metastasio, A.; Mariani, E.; Mattioli, P.; Cherubini, A.; Catani, M.; Cecchetti, R.; Senin, U.; Mecocci, P. Plasma Antioxidants Are Similarly Depleted in Mild Cognitive Impairment and in Alzheimer's Disease. *Neurobiol. Aging* **2003**, *24*, 915–919. [[CrossRef](#)]
112. Carney, J.M.; Starke-Reed, P.E.; Oliver, C.N.; Landum, R.W.; Cheng, M.S.; Wu, J.F.; Floyd, R.A. Reversal of Age-Related Increase in Brain Protein Oxidation, Decrease in Enzyme Activity, and Loss in Temporal and Spatial Memory by Chronic Administration of the Spin-Trapping Compound N-Tert-Butyl-Alpha-PhenylNitron. *Proc. Nat. Acad. Sci. USA* **1991**, *88*, 3633–3636. [[CrossRef](#)]
113. Tran, M.H.; Yamada, K.; Nakajima, A.; Mizuno, M.; He, J.; Kamei, H.; Nabeshima, T. Tyrosine Nitration of a Synaptic Protein Synaptophysin Contributes to Amyloid  $\beta$ -Peptide-Induced Cholinergic Dysfunction. *Mol. Psychiatry* **2003**, *8*, 407–412. [[CrossRef](#)]
114. Guernonprez, L.; Ducrocq, C.; Gaudry-Talarmain, Y.M. Inhibition of Acetylcholine Synthesis and Tyrosine Nitration Induced by Peroxynitrite Are Differentially Prevented by Antioxidants. *Mol. Pharmacol.* **2001**, *60*, 838–846.
115. Lockrow, J.; Prakasam, A.; Huang, P.; Bimonte-Nelson, H.; Sambamurti, K.; Granholm, A.-C. Cholinergic Degeneration and Memory Loss Delayed by Vitamin E in a Down Syndrome Mouse Model. *Exp. Neurol.* **2009**, *216*, 278–289. [[CrossRef](#)]
116. Bruno, M.A.; Leon, W.C.; Fragoso, G.; Mushynski, W.E.; Almazan, G.; Cuello, A.C. Amyloid  $\beta$ -Induced Nerve Growth Factor Dysmetabolism in Alzheimer Disease. *J. Neuropathol. Exp. Neurol.* **2009**, *68*, 857–869. [[CrossRef](#)] [[PubMed](#)]
117. Lan, Z.; Chen, L.; Fu, Q.; Ji, W.; Wang, S.; Liang, Z.; Qu, R.; Kong, L.; Ma, S. Paeoniflorin Attenuates Amyloid-Beta Peptide-Induced Neurotoxicity by Ameliorating Oxidative Stress and Regulating the NGF-Mediated Signaling in Rats. *Brain Res.* **2013**, *1498*, 9–19. [[CrossRef](#)]
118. Lim, S.; Moon, M.; Oh, H.; Kim, H.G.; Kim, S.Y.; Oh, M.S. Ginger Improves Cognitive Function via NGF-Induced ERK/CREB Activation in the Hippocampus of the Mouse. *J. Nutr. Biochem.* **2014**, *25*, 1058–1065. [[CrossRef](#)]
119. Jackson, G.R.; Apffel, L.; Werrbach-Perez, K.; Perez-Polo, J.R. Role of Nerve Growth Factor in Oxidant-Antioxidant Balance and Neuronal Injury. I. Stimulation of Hydrogen Peroxide Resistance. *J. Neurosci. Res.* **1990**, *25*, 360–368. [[CrossRef](#)] [[PubMed](#)]
120. Pan, Z.; Perez-Polo, R. Role of Nerve Growth Factor in Oxidant Homeostasis: Glutathione Metabolism. *J. Neurochem.* **1993**, *61*, 1713–1721. [[CrossRef](#)] [[PubMed](#)]
121. Amara, F.; Berbenni, M.; Fragni, M.; Leoni, G.; Viggiani, S.; Ippolito, V.M.; Larocca, M.; Rossano, R.; Alberghina, L.; Riccio, P.; et al. Neuroprotection by Cocktails of Dietary Antioxidants under Conditions of Nerve Growth Factor Deprivation. *Oxid. Med. Cell. Longev.* **2015**, *2015*, 217258. [[CrossRef](#)]



122. Spear, N.; Estévez, A.G.; Barbeito, L.; Beckman, J.S.; Johnson, G.V.W. Nerve Growth Factor Protects PC12 Cells Against Peroxynitrite-Induced Apoptosis via a Mechanism Dependent on Phosphatidylinositol 3-Kinase. *J. Neurochem.* **1997**, *69*, 53–59. [[CrossRef](#)]
123. Wang, W.; Dow, K.E.; Riopelle, R.J.; Ross, G.M. The Common Neurotrophin Receptor P75NTR Enhances the Ability of PC12 Cells to Resist Oxidative Stress by a TrkA-Dependent Mechanism. *Neurotox. Res.* **2001**, *3*, 485–499. [[CrossRef](#)]
124. Tang, L.-L.; Wang, R.; Tang, X.-C. Huperzine A Protects SHSY5Y Neuroblastoma Cells against Oxidative Stress Damage via Nerve Growth Factor Production. *Eur. J. Pharmacol.* **2005**, *519*, 9–15. [[CrossRef](#)] [[PubMed](#)]
125. Miller, R.; King, M.A.; Heaton, M.B.; Walker, D.W. The Effects of Chronic Ethanol Consumption on Neurotrophins and Their Receptors in the Rat Hippocampus and Basal Forebrain. *Brain Res.* **2002**, *950*, 137–147. [[CrossRef](#)]
126. Song, K.; Na, J.-Y.; Kim, S.; Kwon, J. Rutin Upregulates Neurotrophic Factors Resulting in Attenuation of Ethanol-Induced Oxidative Stress in HT22 Hippocampal Neuronal Cells. *J. Sci. Food Agric.* **2015**, *95*, 2117–2123. [[CrossRef](#)]
127. Guo, C.; Sun, L.; Liu, G.; Zhao, S.; Liu, W.; Zhao, Y. Protective Effect of Nicotine on the Cultured Rat Basal Forebrain Neurons Damaged by B-Amyloid (Ab)25-35 Protein Cytotoxicity. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 2964–2972.
128. Olivieri, G.; Otten, U.; Meier, F.; Baysang, G.; Dimitriades-Schmutz, B.; Müller-Spahn, F.; Savaskan, E. Oxidative Stress Modulates Tyrosine Kinase Receptor A and P75 Receptor (Low-Affinity Nerve Growth Factor Receptor) Expression in SHSY5Y Neuroblastoma Cells. *Neurol. Clin. Neurophysiol.* **2002**, *2002*, 2–10. [[CrossRef](#)] [[PubMed](#)]
129. Kumar, V.; Gupta, A.K.; Shukla, R.K.; Tripathi, V.K.; Jahan, S.; Pandey, A.; Srivastava, A.; Agrawal, M.; Yadav, S.; Khanna, V.K.; et al. Molecular Mechanism of Switching of TrkA/P75 NTR Signaling in Monocrotophos Induced Neurotoxicity. *Sci. Rep.* **2015**, *5*, 14038. [[CrossRef](#)]
130. Ali, T.K.; Matragoon, S.; Pillai, B.A.; Liou, G.I.; El-Remessy, A.B. Peroxynitrite Mediates Retinal Neurodegeneration by Inhibiting Nerve Growth Factor Survival Signaling in Experimental and Human Diabetes. *Diabetes* **2008**, *57*, 10. [[CrossRef](#)]
131. del Pino, J.; Moyano, P.; Anadon, M.J.; García, J.M.; Díaz, M.J.; Gómez, G.; García, J.; Frejo, M.T. SN56 Basal Forebrain Cholinergic Neuronal Loss after Acute and Long-Term Chlorpyrifos Exposure through Oxidative Stress Generation; P75NTR and A7-NAChRs Alterations Mediated Partially by AChE Variants Disruption. *Toxicology* **2016**, *353–354*, 48–57. [[CrossRef](#)]
132. Kim, S.; Kwon, J. [6]-Shogaol Attenuates Neuronal Apoptosis in Hydrogen Peroxide-Treated Astrocytes through the Up-Regulation of Neurotrophic Factors. *Phytother. Res.* **2013**, *27*, 1795–1799. [[CrossRef](#)]
133. Martindale, J.L.; Holbrook, N.J. Cellular Response to Oxidative Stress: Signaling for Suicide and Survival. *J. Cell. Physiol.* **2002**, *192*, 1–15. [[CrossRef](#)] [[PubMed](#)]
134. Hwang, S.-L.; Yen, G.-C. Effect of Hesperetin against Oxidative Stress via ER- and TrkA-Mediated Actions in PC12 Cells. *J. Agric. Food Chem.* **2011**, *59*, 5779–5785. [[CrossRef](#)] [[PubMed](#)]
135. Hamano, T.; Mutoh, T.; Tabira, T.; Araki, W.; Kuriyama, M.; Mihara, T.; Yano, S.; Yamamoto, H. Abnormal Intracellular Trafficking of High Affinity Nerve Growth Factor Receptor, Trk, in Stable Transfectants Expressing Presenilin 1 Protein. *Mol. Brain Res.* **2005**, *137*, 70–76. [[CrossRef](#)] [[PubMed](#)]
136. Jonnala, R.R.; Buccafusco, J.J. Inhibition of Nerve Growth Factor Signaling by Peroxynitrite. *J. Neurosci. Res.* **2001**, *63*, 27–34. [[CrossRef](#)]
137. Iannilli, F.; Sodero, A.O.; Ledesma, M.D.; Dotti, C.G. Oxidative Stress Activates the Pro-Survival TrkA Pathway through Membrane Cholesterol Loss. *Neurobiol. Aging* **2011**, *32*, 1033–1042. [[CrossRef](#)]
138. Zhang, L.; Jope, R.S. Oxidative Stress Differentially Modulates Phosphorylation of ERK, P38 and CREB Induced by NGF or EGF in PC12 Cells. *Neurobiol. Aging* **1999**, *20*, 271–278. [[CrossRef](#)]
139. Scott-Solomon, E.; Kuruvilla, R. Mechanisms of Neurotrophin Trafficking via Trk Receptors. *Mol. Cell. Neurosci.* **2018**, *91*, 25–33. [[CrossRef](#)]
140. Heerssen, H.M.; Pazyra, M.F.; Segal, R.A. Dynein Motors Transport Activated Trks to Promote Survival of Target-Dependent Neurons. *Nat. Neurosci.* **2004**, *7*, 596–604. [[CrossRef](#)]
141. King, S.M. The Dynein Microtubule Motor. *Biochim. Biophys. Acta. Mol. Cell Res.* **2000**, *1496*, 60–75. [[CrossRef](#)]
142. Ogawa, K.; Takai, H.; Ogiwara, A.; Yokota, E.; Shimizu, T.; Inaba, K.; Mohri, H. Is Outer Arm Dynein Intermediate Chain 1 Multifunctional? *Mol. Biol. Cell* **1996**, *7*, 1895–1907. [[CrossRef](#)]
143. Patel-King, R.S.; Benashski, S.E.; Harrison, A.; King, S.M. Two Functional Thioredoxins Containing Redox-Sensitive Vicinal Dithiols from the Chlamydomonas Outer Dynein Arm (\*). *J. Biol. Chem.* **1996**, *271*, 6283–6291. [[CrossRef](#)]
144. Hashemy, S.I.; Holmgren, A. Regulation of the Catalytic Activity and Structure of Human Thioredoxin 1 via Oxidation and S-Nitrosylation of Cysteine Residues. *J. Biol. Chem.* **2008**, *283*, 21890–21898. [[CrossRef](#)]
145. Chaves, R.; Quevedo Melo, T.; D’Unhao, A.; Farizatto, K.; Ferrari, M.F.R. Dynein C1h1, Dynactin and Syntaphilin Expression in Brain Areas Related to Neurodegenerative Diseases Following Exposure to Rotenone. *Acta Neurobiol. Exp.* **2013**, *73*, 541–556.
146. Eiserich, J.P.; Estévez, A.G.; Bamberg, T.V.; Ye, Y.Z.; Chumley, P.H.; Beckman, J.S.; Freeman, B.A. Microtubule Dysfunction by Posttranslational Nitrotyrosination of  $\alpha$ -Tubulin: A Nitric Oxide-Dependent Mechanism of Cellular Injury. *Proc. Nat. Acad. Sci. USA* **1999**, *96*, 6365–6370. [[CrossRef](#)] [[PubMed](#)]
147. Chou, A.P.; Li, S.; Fitzmaurice, A.G.; Bronstein, J.M. Mechanisms of Rotenone-Induced Proteasome Inhibition. *Neurotoxicology* **2010**, *31*, 367–372. [[CrossRef](#)] [[PubMed](#)]
148. Sherer, T.B.; Betarbet, R.; Testa, C.M.; Seo, B.B.; Richardson, J.R.; Kim, J.H.; Miller, G.W.; Yagi, T.; Matsuno-Yagi, A.; Greenamyre, J.T. Mechanism of Toxicity in Rotenone Models of Parkinson’s Disease. *J. Neurosci.* **2003**, *23*, 10756–10764. [[CrossRef](#)]

149. Melo, T.Q.; D'unhao, A.M.; Martins, S.A.; Farizatto, K.L.G.; Chaves, R.S.; Ferrari, M.F.R. Rotenone-Dependent Changes of Anterograde Motor Protein Expression and Mitochondrial Mobility in Brain Areas Related to Neurodegenerative Diseases. *Cell. Mol. Neurobiol.* **2013**, *33*, 327–335. [[CrossRef](#)]
150. Zhang, Y.J.; Xu, Y.F.; Chen, X.Q.; Wang, X.C.; Wang, J.-Z. Nitration and Oligomerization of Tau Induced by Peroxynitrite Inhibit Its Microtubule-Binding Activity. *FEBS Lett.* **2005**, *579*, 2421–2427. [[CrossRef](#)]
151. Fang, C.; Bourdette, D.; Banker, G. Oxidative Stress Inhibits Axonal Transport: Implications for Neurodegenerative Diseases. *Mol. Neurodegener.* **2012**, *7*, 29. [[CrossRef](#)]
152. Olmsted, J.B.; Borisy, G.G. Microtubules. *Annu. Rev. Biochem.* **1973**, *42*, 507–540. [[CrossRef](#)]
153. Matsuyama, S.S.; Jarvik, L.F. Hypothesis: Microtubules, a Key to Alzheimer Disease. *Proc. Nat. Acad. Sci. USA* **1989**, *86*, 8152–8156. [[CrossRef](#)] [[PubMed](#)]
154. Stagi, M. Breakdown of Axonal Synaptic Vesicle Precursor Transport by Microglial Nitric Oxide. *J. Neurosci.* **2005**, *25*, 352–362. [[CrossRef](#)] [[PubMed](#)]
155. Hirokawa, N.; Noda, Y.; Tanaka, Y.; Niwa, S. Kinesin Superfamily Motor Proteins and Intracellular Transport. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 682–696. [[CrossRef](#)] [[PubMed](#)]
156. Tanaka, Y.; Niwa, S.; Dong, M.; Farkhondeh, A.; Wang, L.; Zhou, R.; Hirokawa, N. The Molecular Motor KIF1A Transports the TrkA Neurotrophin Receptor and Is Essential for Sensory Neuron Survival and Function. *Neuron* **2016**, *90*, 1215–1229. [[CrossRef](#)] [[PubMed](#)]
157. Yamashita, N.; Joshi, R.; Zhang, S.; Zhang, Z.-Y.; Kuruvilla, R. Phospho-Regulation of Soma-to-Axon Transcytosis of Neurotrophin Receptors. *Dev. Cell* **2017**, *42*, 626.e5–639.e5. [[CrossRef](#)] [[PubMed](#)]