Mini Review

Signaling of the neurotrophin receptor p75 in relation to Alzheimer's disease

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A B S T R A C T

The cellular mechanism of neuronal apoptosis in Alzheimer's disease (AD) is poorly understood. Many hypotheses have been put forth to explain the underlying reason for neuro-degeneration in AD. Here, it is demonstrated that all neurotrophins that activated p75, without co-activation of the relevant Trk co-receptor, mediated apoptosis in hippocampal neurons. Thus, proneurotrophins and amyloid β peptides (Aβ) can induce p75-mediated apoptosis in hippocampal neurons since they do not bind or activate Trk receptors. Based on the combined effects of aging, proneurotrophins, neurotrophins, and Aβ, a novel model of pathogenesis in AD is proposed. This mini-review explores the ligand and cell type based signaling pathways of the neurotrophin receptor p75 relating to Alzheimer's disease.

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Overview

Apoptosis, cell survival and differentiation are controlled by two transmembrane glycoproteins, the neurotrophin receptor p75 and tropomyosin receptor kinase (Trk) [1]. p75 is a member of the tumor necrosis factor (TNF) super family of receptors [2–4], with multiple functions. p75 is implicated in cellular apoptosis, cell survival and differentiation, neurite outgrowth [5–7], Schwann cell myelination [8], and Schwann cell development [3]. Trk is a ligand-selective tyrosine kinase receptor [9], and interacts with p75 to signal the neuronal cell survival or apoptosis [1]. However, TrkA, subtype of Trk is neuroprotective in several cell lines [10,11]. The various functions of p75 depend on the type of ligand bound to it, the cell type in which it is expressed and the presence or absence of Trk receptor. p75 induces the neurotrophin nerve growth factor (NGF) mediated survival in neuronal cells expressing TrkA [12]. Moreover, neurons expressing p75 without co-expressing Trk underwent apoptosis upon NGF treatment [2]. In other words, when there is reduction or absence of Trk activation, apoptosis occurs upon NGF binding to p75 [6,10]. However, expression of p75 without Trk is not enough to elicit apoptosis in astrocytes and oligodendrocytes; suggesting that the fate of cells depend not only upon Trk expression and possibly on other factors [10].

One of the early indicators of Alzheimer's disease is the death of cholinergic neurons in the basal forebrain which express the highest level of p75 in the adult brain [13,14]. The disease also leads to the loss of cholinergic neurons in the cerebral cortex, septum pel-lucidum, and the hippocampus, which is critical for memory [15]. Previous reports suggested that the neuronal loss observed in the basal forebrain of Alzheimer's patients is p75 dependent [9,14]. Similar to neurotrophins, amyloid β (Aβ) also serves as a p75 ligand [12]. The pathological accumulation of Aβ (1–42) is a hallmark of Alzheimer's disease [16]. TrkA, reduces the β-cleavage of amyloid precursor protein (APP) to generate amyloid β peptide while p75 enhances the cleavage [17], and Aβ was observed to cause p75-mediated neurotoxicity in several cell lines [13,14,18]. Decreased levels of TrkA are observed in basal forebrain cholinergic neurons of Alzheimer’s patients [19,20], along with increased levels of proneurotrophins in their parietal cortex [21]. This opens up the possibility that neuronal death in the Alzheimer’s disease can also be attributed to proneurotrophins mediated apoptosis through p75 signaling [22]. This mini-review will explore the structure, functions, and cellular signaling pathways of p75 in relation to Alzheimer’s disease.

Structure of the neurotrophin receptor p75

The structural organization of the neurotrophin receptor p75 is composed of three main parts. First, it has the cysteine-rich extracellular repeats that form four ligand-binding sites [5,13]. The second part is made of a single pass domain that crosses the plasma membrane to link with the intracellular domains [13,23]. Lastly, the intracellular component of the p75 receptor is composed of a chopper domain and TNF-like death domain [13]. The structure of the p75 neurotrophin receptor is illustrated in Fig. 1. The death domain was observed to induce apoptotic signaling similar to that
of TNF and Fas ligand mediated apoptosis [5,23,24]. Just like APP, p75 is cleaved by β and γ secretases [13,25,26].

Neurotrophins as p75 and Trk ligands

The p75 receptor binds a broad variety of ligands, while Trk receptor family members are very selective. All four neurotrophins nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT 3) and neurotrophin 4 (NT 4) bind to p75 with the similar affinity, but different kinetics [12]. However, the subtypes of the p75 co-receptor Trk selectively bind specific types of neurotrophins [27]. For instance, NGF exclusively binds to TrkA, while BDNF and NT 4 bind to TrkB, and NT 3 to TrkC [6,10,12]. Other subtypes of Trk are truncated forms of TrkB and TrkC which lack kinase activity in their intracellular kinase domain [2,28]. The main difference between the subtypes of Trk relies in their extracellular domain. The difference in residues in the extracellular immunoglobulin like domain coupled with three leucine-rich motif causes the selective binding to specific types of neurotrophins [13,29].

Intracellular mediators and cellular signaling of p75 in neuronal cells

A variety of ligand dependent signaling pathways have evolved for the maintenance of cellular integrity vs. induction of apoptosis. Nonetheless, the general consensus is that to signal apoptosis, p75 activates c-jun N-terminal kinase (JNK) [10] and caspases which results in ceramide production [2,7]. In contrast, signaling survival is through the activation of the nuclear factor kappa B (NF-kB) [3,7,13]. The specific cell type adds another dimension of complexity to signaling cascade initiated by p75. Therefore, the following section summarizes the different ligand-based and cell specific signaling pathways demonstrated by p75 and Trk receptor in neurons, oligodendrocytes, and Schwann cells.

Neurotrophin-dependent signaling

The type of cell often determines the interacting molecules and the final outcome of the signaling pathway. Defreitas et al. [9] observed that when TrkB and TrkC expressing embryonic neurons were treated with BDNF and NT 3, they increased the survival rate by twofold. The subsequent treatment of the same population of cells with NGF resulted in high levels of NGF competing BDNF and NT 3, the p75 neurotrophin receptor leads to decrease their survival signals [9]. However, primary sympathetic neurons expressing p75 and TrkA, but not TrkB, undergo apoptosis upon BDNF binding [2]. Furthermore, Yamashita et al. [30] observed that NGF-dependent outgrowth of ciliary neurons was mediated through RhoA association with p75.

Central nervous system neurons

p75 neurotrophin receptor has no intrinsic enzymatic activity so it depends on its interaction with several proteins to signal the cascade for neuronal survival [8]. The NGF-dependent pathway in cells expressing both p75 and TrkA is characterized by the activation of myeloid differentiation primary response gene (88) protein (MyD88) upon NGF binding to p75 [6,31,32]. MyD88 then binds to IRAK; which in turn recruits TNF receptor associated factor 6 (TRAF6), an ubiquitin ligase enzyme [33]. TRAF6 is a member of family of six TRAFs notable for the ability to bind members of the TNF receptor super family [34]. The p75 neurotrophin receptor is a substrate of TRAF6 ubiquitination [8]. TRAF6 interacts with p62, the shuttling factor for delivery of poly-ubiquitinated substrates, leading to NF-kB activation [31,33]. The cell survival engendered by this cascade is not only by NF-kB activation, but also due to suppression of p75-mediated death signals acting through JNK [35]. This process is especially of interest; since in Alzheimer’s disease, the expression of p75 receptor is higher in cortical neurons and the level of TrkA is lower [19]. The same type of neuronal cells can also mediate survival through TrkA-dependent signaling. Upon NGF binding, TrkA mediates cell survival through Ras-mediated pathway leading to mitogen activated protein kinase (MAPK) and phosphoinositide-3 kinase (PI3K) [36,37].

Alternatively, the p75-mediated neuronal apoptotic pathway is mediated by several interacting molecules. Activation and cleavage of p75 upon ligand binding, via metalloproteases [18], leads to the ubiquitination and nuclear translocation of the neurotrophin receptor-interacting factor (NRIF) [4,38], phosphorylation of JNK [4,38,39], phosphorylation and oligomerization of the BH3-domain-only family member (Bad) [36,39], and activation of caspases 9, 6, and 3 [38,39].

Oligodendrocytes

Similar to neurons, adult oligodendrocytes express p75, TrkA, truncated TrkB [28] and TrkC [7]. Oligodendrocytes expressing both p75 and TrkA activate the MAPK mediated cascade to promote NGF-dependent survival [1,28]. TrkA also promote cell survival by inhibiting the death domain activity of the p75 [1]. Inhibition of apoptosis by TrkA is further demonstrated through the suppression of NGF-dependent sphingomyelin hydrolysis to form ceramides [6]. This is consistent with the p75 death domain inhibition since ceramides synthesis is strongly associated with p75-mediated apoptosis [2,7]. NGF-dependent survival signal increases with the presence of p75 in TrkA expressing oligodendrocytes [1]. In contrast, cultured oligodendrocytes expressing only p75 without co-expressing TrkA were observed to undergo apoptosis upon NGF treatment [5,40]. NGF-dependent apoptosis in oligodendrocytes is mediated by Rac GTPase and JNK3 leading to ceramides production and apoptosis [7] through caspase 1 activation [24].

The stimulation of TrkB with BDNF and that of TrkC by NT 3 did not induce Rac GTPase dependent apoptosis [7]. TrkC is expressed in both developing or progenitor oligodendrocytes [28] and adult.
oligodendrocytes [7]. The removal of NT 3 sources from the developing optic nerve and astrocytes decreases the number of differentiating progenitor oligodendrocytes to mature ones [28]. This observation implies that NT 3 mediated signaling is crucial for the differentiation of progenitor oligodendrocytes into adult ones [28].

Schwann cells

p75 mediates multiple processes in Schwann cells including survival, apoptosis, development and migration [3]. The NGF-dependent survival pathway requires activation of the TRAF6 [3,34] and or the receptor-interacting protein 2 (RIP2) [3]. However, TRAF6 is also activated in the apoptosis signaling of Schwann cells [34]. The presence of TrkA seems not to be the determining factor leading to either survival or apoptosis in Schwann cells [3]. Nonetheless, it is worth noting that during nervous tissue stress or injury and removal of axons induces the expression of high levels of NGF and p75 by Schwann cells suggesting a protective role of p75 against cell death in early injury [3].

p75-mediated death without cognate Trk receptor

Expression of Trk receptor along with p75 is neuroprotective. This was observed by W.J. Friedman [10] who found a statistically significant difference in the neurotrophin mediated apoptosis between a culture of hippocampal neurons expressing both p75 and Trk receptor vs. those expressing only p75 but not Trk receptor [10]. It has been shown that 88% of NGF treated neurons that lacked TrkA underwent apoptosis compared to only 12% of NGF treated neurons that expressed TrkA. Likewise, 86% of BDNF treated neurons that lacked TrkB went apoptotic while 14% of the BDNF treated cells with TrkB had the same fate. Similar statistics were obtained for NT 3 (88% vs. 12%) and NT 4 (84% vs. 16%) treated hippocampal cells [10]. Similarly, retinal neurons expressing p75, without TrkA underwent NGF-dependent apoptosis [5,11]. Apoptosis appears to be promoted by ligands that activate p75 without activating the relevant Trk receptor [10,38].

Proneurotrophin and Aβ dependent signaling

Proneurotrophins

Proneurotrophins functions as ligands to p75, but not to Trk receptor. For instance pro-NGF, activates p75 without co-activating TrkA in the basal forebrain and induces neuronal death [22]. Likewise, pro-BDNF was observed to induce apoptosis in the same population of forebrain neurons [22]. Interestingly, there is an increase in proneurotrophin levels in neurodegenerative diseases, such as Alzheimer’s [18,41] and in the brain after injury or stress [41,42]. However, pro-BDNF and pro-NGF levels are not increased in the cerebrospinal fluid after injury [41]. Thus, some researchers inferred that cholinergic neuronal loss seen in Alzheimer’s disease patients is due to this relative increase in proneurotrophins levels, especially pro-NGF [22,41].

Amyloid β peptide (Aβ)

In Alzheimer’s disease, Aβ is produced through the sequential proteolysis of amyloid precursor protein (APP) at β and γ sites [15,25,26] by β and γ secretases, respectively [13]. Aβ comes in variable peptide length ranging from 39 to 43 amino acids [15,18,23]. Over the years, Aβ was proposed to act as a ligand to many proteins [23], but its role as a p75 ligand appears to be the most relevant to AD. The binding of Aβ chains, especially amino acid within the 29–35 to p75, has been shown to induce neurotoxicity [13].

Similar to proneurotrophins, Aβ binds to the p75 receptor, but not TrkA, and induces apoptosis [14,26] through the receptor’s intracellular death domain signaling mechanism [23]. The p75-mediated Aβ cytotoxicity mechanism involves the downstream activation of p75 intracellular death domain [13]. The death domain in turn activates Gcα [23] which leads to JNK phosphorylation [13,23]. Although there are many pathways hypothesized, most of the sources found the terminal outcome of this process to be cell death [13,18,23,43]. These findings are also consistent with the results of Sotthibundhu and colleagues who found that hippocampal neurons became apoptotic after Aβ1–42 treatment [18].

![Fig. 2](image-url) This figure illustrates the role of neurotrophins. Aβ and proneurotrophins in pathogenesis of AD in a cyclic manner. The normal decrease of Trk level in aging along with the increase in p75 activation results in apoptosis and ceramides production in neurons. Ceramides then stabilize β secretase, which cleaves APP to Aβ. High level of Aβ and proneurotrophins will then activate p75, but not Trk thus leading to neuronal apoptosis.
Is neuronal loss in Alzheimer’s caused by Aβ, proneurotrophin, or neurotrophin?

According to survey published in 2003, by Hebert and colleagues, aging is the single most important risk factor for Alzheimer’s [44]. In normal aging there is a gradual increase in the expression of p75 receptor accompanied by a decrease in TrkA expression [15,45]. Decrease in the TrkA to p75 ratio and coordinate regulation of neurotrophins activates sphingomyelinase, and enhances production of ceramides [15,45]. High levels of ceramides can act as second messenger to induce apoptosis [5], and stabilize BACE1 or β secretase [15,45]. β secretase then cleaves APP to form Aβ peptide [13,15,26,45,46]. Aβ acts as a ligand to p75 promoting cellular apoptosis in rat cortical neurons and human epidermal melanocytes [14]. This apoptosis is mediated through JNK, caspases 9, 6, and 3, [13,17] and leads to more ceramide production [13,17,47]. As the disease advances, there is an increase in the proneurotrophin levels [22], especially pro-NGF, and decrease in the TrkA receptor. JNK, caspases 9, 6, and 3,[13,17] and leads to more ceramide production [13,17,47]. As the disease advances, there is an increase in the proneurotrophin levels [22], especially pro-NGF, and decrease in the TrkA to p75 ratio may further enhance ceramide production by increasing the activation of p75 via neurotrophins, proneurotrophins, or Aβ without co-activating the relevant Trk. This process is demonstrated in Fig. 2. In brief, Aβ, neurotrophins, and proneurotrophins all contribute to the pathology and progression of the Alzheimer’s disease in a cyclic manner.

Conclusion

Hippocampal neurons undergo neurotrophin-dependent p75-mediated apoptosis in the absence of Trk co-activation. Ligands that activate p75 but not Trk, such as Aβ and proneurotrophins, may contribute to the pathogenesis of AD. However, it remains to be determined which of these ligands has the most impact in disease pathogenesis. It is also worth determining whether reducing level of such ligand can alleviate pathogenesis of AD.

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