

## Multiple Functions of the P75 Neurotrophin Receptor in the Nervous System

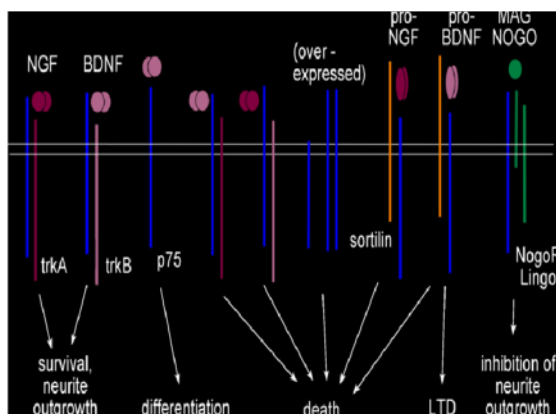
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Article information	Abstract
<p>Article history: Received: 15 June 2011 Accepted: 25 Aug 2011 Available online: 29 Dec 2011</p> <p>Keywords: Camellia sinensis Liver Spleen Electromagnetic field Balb/C rat</p> <p>*Corresponding author at: Department of biochemistry, Institute of biochemistry and biophysics, University of Tehran, Tehran, Iran. E-mail: firouzi@ibb.ut.ac.ir</p>	<p><b>Background:</b> The P75 neurotrophin receptor (p75<sup>NTR</sup>) is a transmembrane protein that binds the nerve growth factor (NGF) and implements multiple functions in the nervous system. It is expressed widely during the development of the nervous system although its expression is dramatically decreased at adulthood. Though the P75 neurotrophin receptor has been identified more than 35 years ago, our knowledge about its structure and function has barely increased.</p> <p><b>Materials and Methods:</b> In this review various methods are used to search databases and reliable scientific resources have been reviewed to give an up-to-date panoramic picture of the protein expression, structure, function, and its interaction with other known molecules.</p> <p><b>Results:</b> P75<sup>NTR</sup> not only in neurons but also in various types of glial cells is expressed. In addition to NGF, this receptor can also bind the tropomyosin kinase receptors. Some pathological conditions such as neurodegenerative diseases and nerve damages are followed by the considerable increased expression of p75<sup>NTR</sup>.</p> <p><b>Conclusion:</b> In this study, the role of p75<sup>NTR</sup> in the nervous system of human beings has been investigated and it has been illustrated that how spinal cord repair can improve by blocking of p75<sup>NTR</sup>. It seems that in addition to p75<sup>NTR</sup>, some other homologues are also involved in this pathway. Further studies are required to elucidate more details about the role of p75<sup>NTR</sup> in the development and function of the nervous system.</p> <p>Copyright © 2012 Zahedan University of Medical Sciences. All rights reserved.</p>

### Introduction

In 1973, the P75 neurotrophin receptor (p75<sup>NTR</sup>) was recognized as a nerve growth factor (NGF) receptor by Herrup and Shooter [1]. Later, it was shown that this receptor could bind other neurotrophins including BDNF, NT3 and NT4/5; moreover, the ability of p75<sup>NTR</sup> in binding different precursors of neurotrophins was approved [2-4] (Fig. 1).



**Figure 1.** Various co-receptors in binding with various ligands and their different functions

However P75<sup>NTR</sup> belongs to Tumor Necrosis Factor Receptors (TNFR) family, It is somehow different from them. Its molecular weight is 75 KDa and has also some functions in immunity and vascular system.

P75<sup>NTR</sup> expression is regulated developmentally. It is highly expressed in the developing nervous system, while it decreases dramatically over adulthood. In adult people, it can be found in various deals in different parts of the nervous system. On the other hand, its expression is increased during the pathological conditions and induces apoptosis. It has been demonstrated that the expression of the P75 receptor is minimized across the afferent sensory axons of the spinal cord, dorsal root ganglion (DRG) and visual cells of adult rats, while it can be found in measurable levels cerebellum and cortex [5].

It seems that P75<sup>NTR</sup> expression is regulated by intracellular mechanisms. Santee et al. specified the gene structure of the human P75<sup>NTR</sup> [6] and showed that this gene is made of 75000 base pairs which has 10 exons and 9 introns. Its structure is similar to TNFRs [7] and has three domains including extra-membrane, inter-membrane and intra-membrane. The extra-membrane domain has four repetitive sequences which are enriched with cysteine and negative charge. The neurotrophins binding site is located in the third and fourth repetitive sequences enriched with cysteine, because the receptors without these two sequences are not able to bind neurotrophins [8]. Glycosylation process is conducted in two forms: N and O [9].

P75<sup>NTR</sup> is the sixteenth member of TNFR family which its ligand binding site is located in the extracellular repetitive region enriched with cytosine and it is conserved severely. The death domain is located in the intra-membrane domain of P75<sup>NTR</sup>. This domain is the

type II of the death domain, so p75<sup>NTR</sup> is different from other TNFRs which contain the type I of the death domain. It is not able to conduct self association [10]; in other words, it follows a different mechanism to induce apoptosis[11].

The inter-membrane domain of p75<sup>NTR</sup> has a ligand binding side in N-Terminal [10] which likely plays an important role in the signal transduction. The intra-membrane or cytoplasmic domain of P75<sup>TNR</sup> does not possess any enzymatic properties that can be considered as another difference of this receptor with Tropomyosin kinase (TrK) receptors; hence TrK, as a neurotrophin receptor, has higher and more specific affinity to bind neurotrophins rather than p75<sup>NTR</sup> [12].

P75<sup>NTR</sup> is considered as a co-receptor for TrK which improves neurons and neuroglia cells survival. In PC12 cells, binding P75<sup>NTR</sup> to TrK induces the formation of the growth cone and cell survival by NGF [13]. In mouse hippocampal cells of p75 mutant (P75 (-/-)), activation of TrKA by NGF is trivial and non-quantifiable. Moreover, it has been illustrated that P75<sup>NTR</sup> increases the binding capacity of TrK in order to help NGF for better transduction of neurotrophins signals which are necessary to boost neurons survival.

Zaccaro showed that P75<sup>NTR</sup> is able to expose certain regions of the protein to bind neurotrophins through changing subdomain in TrK and hence to increase binding capacity to TrK from 10<sup>-9</sup>M to 10<sup>-11</sup>M [14]. P75<sup>NTR</sup>'s crystal structure has shown that one molecule of P75<sup>NTR</sup> can bind two molecules of NGF. It helps P75<sup>NTR</sup> to bind another co-receptor like TrK to form a non-identical complex [15]. This idea has roots in similarity between extracellular domains of P75<sup>NTR</sup> and TNF receptor which often facilitates binding of a trimer to the ligand. Wehrmen et al. specified the extracellular 3D structure of TrK and NGF and depicted it like a crab [16]. However, its relation with P75<sup>NTR</sup> has not been cleared yet. They also indicated that the TrK membrane heterodimer and P75<sup>NTR</sup> as well as NGF-TrKA heterodimer are found in a form of an oligomer across the cellular level, while there are not any documents to approve the direct interaction between P75<sup>NTR</sup> and TrKA.

Since P75<sup>NTR</sup> acts as a co-receptor for the TrK receptor in the cell survival signaling pathway, it is hypothesized that neurotrophins can induce apoptosis when act independently of TrK association, particularly when TrK is not expressed. This idea was enforced by observing apoptosis occurrence in various cell types in which TrK is not expressed or TrK receptor totally had been removed.

Frade (1996) showed that during development, the produced NGF in cells causes the death of the visual neurons in which P75<sup>NTR</sup> has been expressed [17], while the neurons survive with the expression of PrkA. Thus, if P75<sup>NTR</sup> is removed, many cells will be conserved against apoptosis. Therefore, the dual function of P75<sup>NTR</sup> in two opposite directions of cell survival and apoptosis were studied either in vivo or in vitro.

Ceramide, signal regulated kinase, RAS, Jun N-Terminal Kinase (JNK), ERK which usually are posed as stress-activated protein kinase (SAPK) are located in the

downstream side of P75<sup>NTR</sup> across the signaling pathway (Fig.2)[4]

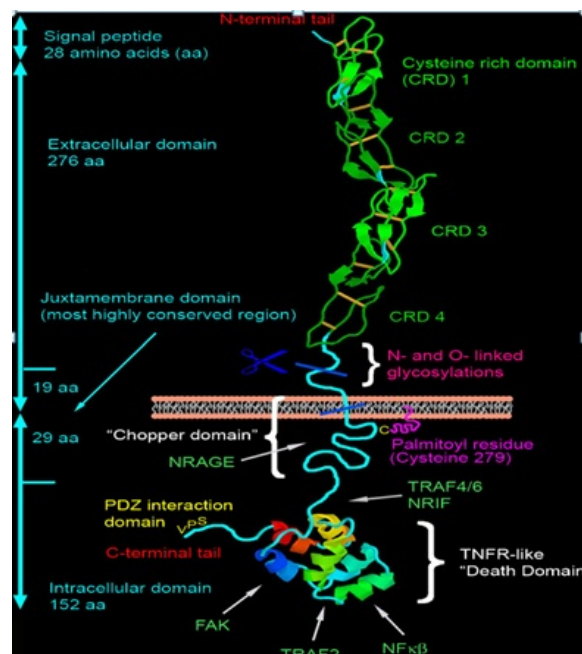


Figure 2. Protein structure of P75<sup>NTR</sup>

Ceramide is a cell membrane unit which can induce growth or apoptosis as a second messenger. For ceramides, TNF receptor acts as a molecule in the apoptosis signaling pathway.

For instance, the aggregation of ceramids is caused by NGF in a neuroblast cell line which expresses P75<sup>NTR</sup>, while it does not happen in cells that only express TrK [18]. The oligodendrocytes in which only P75<sup>NTR</sup> is expressed and there is no TrK expression, adding NGF induce ceramide generation and finally apoptosis [19].

Frago et al indicated that the reduction of endogenous ceramide can inhibit inner ear cells from apoptosis [20]. The activity of TrK induces auto phosphorylation of tyrosine subunit in the intracellular section and activates RAS/ERK path which is followed by neurite outgrowth, elongation and branching.

Death domain of P75<sup>NTR</sup> has two tyrosine subunits: y336 and y337 which are phosphorylated after activation of P75<sup>NTR</sup>, then Ras is activated adaptor proteins for TrK receptors [21]. Ceramide [22] and Ras [23] cause neuron survival through activation Phosphatidylinositol 3-Kinase (PI3-K) which has been bound the juxtamembrane sequence of the cytoplasmic area of P75<sup>NTR</sup>. Therefore, P75<sup>NTR</sup> induces cell survival through a new signaling pathway which is resulted in activation of PI3k-Akt (Phosphatidylinositol 3-Kinase-Ser/Thr-specific protein kinase).

Many specialists have attributed JNK to apoptosis and have indicated that the function of JNK is induced by binding neurotrophins to P75<sup>NTR</sup>. In culture of the sympathetic neurons the enhancement of JNK activity and apoptosis is observed after the binding of neurotrophins to

P75<sup>NTR</sup>. The role of JNK pathway in P75<sup>NTR</sup> signaling prevents NGF-associated apoptosis through inhibiting JNK activity [24].

Another kinase which is activated by P75<sup>NTR</sup> is NF-KB and it is posed as an anti-apoptotic factor. In Schwann cells, the expression of P75<sup>NTR</sup> is facilitated through binding NGF which activates NF-KB [25], while NF-KB activity in oligodendrocytes of a newborn mouse has induced apoptosis [26]. In spite of the important role of NF-KB and JNK in the neuron survival and apoptosis, confining only to these two pathways is impossible.

Although P75<sup>NTR</sup> does not possess any enzymatic properties to induce formation of the intracellular connections, other proteins should be employed to induce transduction of signals of P75<sup>NTR</sup> to the downstream factors such as NF-KB and JNK. Such proteins are: (NADE) NT-Associated cell Death Executor, TNF Receptor Associated Factors (TRAFs), Neurotrophin Receptor Interacting Factor (NRIF), Receptor Interacting Protein2 (RIP2), Neurotrophin Receptor Associated MAG homologue (NRAGE), Schwann Cell-1 (SC-1) [27].

### The inhibitory function of P75<sup>NTR</sup>

This fact that neurons of the central nervous system (CNS) naturally are not able to regenerate themselves after injury has been broadly accepted and there are various reasons to justify it including, scar formation, development of myelin inhibitors and the reduction of internal potential for regeneration; thus Schwann cells in the peripheral nerves are used to repair the CNS including the spinal cord injury [28, 29].

Myelin inhibitory molecules including Nogo, Myelin Associated Glycoprotein (MAG), Oligodendrocyte Myelin glycoprotein (OMgp) bind a single receptor called Nogo66 (NgR). However, since NgR does not have any intracellular domains, it cannot induce all of these changes solely unless it forms NgR-Lingol-P75 complex [30]. But the question is that which signaling pathway causes the collapse of the growth cone? Activation of Ras homologue, i.e. RhoA has been repeatedly posed in various studies as a factor to inhibit repairing [31]. In some studies which NgR, p75<sup>NTR</sup>, RhoA have been suppressed by siRNA, the function of myelin inhibitors have also been prevented [32], though it is not possible to indicate that RhoA binds directly the NgR-Lingol-P75<sup>NTR</sup> complex.

Yamashita indicated that the direct interaction between Rho-Guanine dissociation inhibitor (Rho-GDI) and P75<sup>NTR</sup> activates RhoA. RhoA usually binds Rho-GDI and cannot be activated by Guanine Exchange Factors (GEF). But when myelin binds the NgR-Lingol-P75<sup>NTR</sup> complex, P75<sup>NTR</sup> can bind the fifth helix of Rho-GDI and generate RhoA from Rho-GDI. When GEF is activated, Rho A activates Rock (Rho activated kinase) and depolarize the actin filament and finally causes the collapse of the growth cone [33]. P75<sup>NTR</sup> binding with neurotrophins decreases expression of RhoA and elongates the growth cone [34]. P75<sup>NTR</sup> plays vital roles in

neuron growth and innervation, so if P75<sup>NTR</sup> is removed completely, both growth and innervation will be affected [36]. However, it is not still clear that whether TrK receptor is active in repairing or not.

Domeniconi showed that binding MAG with cerebellum neurons induces the function of Secretase- and segregation of the proteolytic domain of P75<sup>NTR</sup> which is necessary for Rho activity and for inhibition of TNF-  $\alpha$ -Converting enzyme (TACE) [35]. Ahmed approved the induction of intra-membrane proteolysis in the pathway of axon growth inhibition [36].

### Function of P75<sup>NTR</sup> in the glial cells

Expression of P75<sup>NTR</sup> in various glial cells, particularly during the development of the nervous system and also after its damages is increased. There are few studies about the function of P75<sup>NTR</sup> in the glial cells which is due to complicated functions of P75<sup>NTR</sup>. P75<sup>NTR</sup> signaling has been studied mostly in Schwann cells [31]. Schwann cells express a great deal of P75<sup>NTR</sup> during development and repair of the peripheral neurons, though the exact role of P75<sup>NTR</sup> in axons myelination process has not been discovered so far. Cosgaya indicated that the myelination is increased in the co-culture of DRG neurons along with the Schwann cells by endogenous BDNF through P75<sup>NTR</sup> [37]. Moreover, Chan stated that Par-3 polarity protein and P75<sup>NTR</sup> are necessary to facilitate interaction between axon and glia and also myelination of axons [38]. The function of P75<sup>NTR</sup> in culture of Schwann cells both in vitro and in vivo as well as its effect on re-myelination of the damaged axons of the peripheral neurons has been studied. In a new animal model (Nude mouse) in which Schwann cells were deficient of P75<sup>NTR</sup>, Tomita indicated that if the Schwann cells of p75 (-/-) are transplanted to such mice, their axons will lose their myelin and retrograde will be slow after even 6-10 weeks of damage [39]. Sachs et al. used a new mechanism, which is regulated by P75<sup>NTR</sup> in the pathological conditions, to analyze dissociation of cAMP and formation of scar caused by damages. They illustrated that P75<sup>NTR</sup> expression rate has been increased in the damaged tissue which it inhibits fibrinolysis through decreasing the serine-protease, which is the activator of tissue plasminogen, and increasing inhibition of plasminogen activator [40].

It has been demonstrated that P75<sup>NTR</sup> induces apoptosis in oligodendrocytes culture which is followed by activity of Rac-GTPase, phosphorylation of JNK and activity of Caspase. Similarly, for in vivo conditions, P75<sup>NTR</sup> causes apoptosis in oligodendrocytes when the spinal cord has been damaged.

Therefore, P75<sup>NTR</sup> plays a different role in myelination of the peripheral nerves in comparison with the central nervous system (CNS). It has been demonstrated that P75<sup>NTR</sup> is expressed in the astrocytes population of adult mice in CNS and its expression is dramatically increased in every nerve damage. This finding indicates the role of P75<sup>NTR</sup> in the pathological conditions. Although increased

expression of P75<sup>NTR</sup> sets astrocytes culture where scar is formed near the CNS damaged area.

## Results

Our ever-increasing information about either structure or function of P75<sup>NTR</sup> indicates how complicated it is in the nervous system; however, it can be helpful in discovering other related molecules which is involved in the signaling pathway and recognizing the available mechanisms.

This review showed that how P75<sup>NTR</sup> acts in the nervous system and how the inhibition of P75<sup>NTR</sup> improves repairing of the damaged spinal cords; likewise, it has

been emphasized that other homologues in addition to P75<sup>NTR</sup> must be involved in this pathway. For instance, NRH2 may be one of such homologues which enhance binding of TrK to NGF. Troy is another member of TNF and TAJ receptor family which is considered as a homologue for P75<sup>NTR</sup> and it seems that it plays an important role in inhibiting of the repairing; its expression in the nervous system is higher than expression of P75<sup>NTR</sup>. Further studies will specify the role of P75<sup>NTR</sup> in the development and function of the nervous system

## Conflict of Interest

No conflict.

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