

## p75NTR as a Therapeutic Target for Neuropsychiatric Diseases

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**Abstract:** The p75 neurotrophin receptor (p75NTR) was originally identified as a low-affinity receptor for neurotrophins. Recent studies have revealed that p75NTR can promote cell death or survival and modulate neurite outgrowth depending on the operative ligands and co-receptors. Up-regulation and ligand activation of p75NTR have been shown to be involved in neuronal cell death in cultured cells and animal models of neurodegenerative diseases. The levels of proneurotrophins, which bind to p75NTR to promote neuronal death, have been found to be increased in postmortem brains of patients with Alzheimer's disease. Furthermore, there is some evidence for the involvement of this molecule in psychiatric diseases, such as depression and schizophrenia. Mice lacking *p75NTR* have been shown to have several alterations in central nervous system and cognitive function. Notably, recent progress in genome-based drug discovery has enabled the identification of peptides and non-peptide small molecules targeting p75NTR, which may be potentially beneficial in the treatment of neuropsychiatric diseases. In this review, we focus on recent findings on p75NTR as a therapeutic target for neuropsychiatric diseases.

**Keywords:** p75NTR, neurotrophin, proneurotrophin, depression, schizophrenia, Alzheimer's disease, drug discovery, knockout (KO) mouse.

### INTRODUCTION

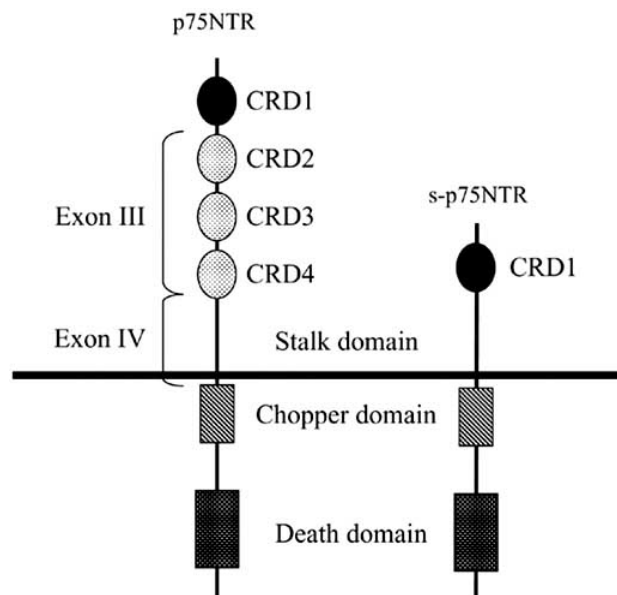
p75NTR was identified as a receptor for neurotrophins, namely, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4/5 (NT4/5), and cloned as a type I transmembrane protein, with its molecular weight of 75 kDa being glycosylated through both N- and O-linkages in the extracellular domain [1-5]. Neurotrophins influence numerous cellular activities such as proliferation, growth, differentiation, and regeneration [6]. The most extensively studied neurotrophin, BDNF, for example, has been implicated in Alzheimer's disease [7-9] and psychiatric diseases such as depression [10, 11] and schizophrenia [12, 13]. It is therefore feasible to speculate that the pan-neurotrophin receptor, p75NTR, might play critical roles in the pathogenesis of neuropsychiatric diseases. It might be a possible target molecule for the treatment of such diseases, although little attention has thus far been paid to p75NTR.

### MOLECULAR OUTLINE

Human p75NTR is a 427 amino acid protein containing a 28 amino acid signal peptide, four extracellular cysteine-rich domains (CRD1 to CRD4), an extracellular stalk domain, a single transmembrane domain, and a 155 amino acid cytoplasmic domain. There is a short splicing variant of p75NTR, which will be described in more detail later (Fig. 1). p75NTR binds neurotrophins through interactions with the CRDs, each with six cysteine residues at conserved positions [14, 15]. The extracellular stalk domain is serine/threonine-rich and contains O-linked glycosylation sites [16]. The cytoplasmic juxtamembrane region, called the chopper domain, has been found to be necessary and sufficient to initiate neural cell death [17]. The second half of the intracellular domain is the death domain whose activation induces apoptosis [18, 19]. Signaling mediators, which are activated subsequent to ligand binding to p75NTR, include ceramide [20], nuclear factor  $\kappa$ B (NF- $\kappa$ B) [21], Akt (also known as protein kinase B) [22], c-Jun N-terminal kinase (JNK) [23], and caspases [17].

p75NTR is a receptor for all mature neurotrophins (NGF, BDNF, NT3, and NT4/5) and immature proneurotrophin forms [24] (Fig. 2). Neither tropomyosin-related kinase A (TRKA) nor p75NTR forms a high-affinity binding site when expressed alone, whereas coexpression of the two receptors results in formation of

high-affinity mature neurotrophin binding sites [25]. In forming a complex with TRK receptors (TRKA, TRKB, and TRKC) for the mature neurotrophins, p75NTR modulates the affinity and activity of these kinases that promote neuronal survival [25-30]. The high-affinity binding of proneurotrophins to p75NTR is mediated by interaction of the receptor with a co-receptor, sortilin, which is thought to promote apoptosis [31, 32]. p75NTR can also bind ligands other than neurotrophins, for example, amyloid beta [33], prion peptides (PrPs) [34], and rabies virus glycoprotein (RVG) [35, 36]. Moreover, it interacts with co-receptors other than TRKs and sortilin, for example, the NOGO receptor (NOGOR) and leucine rich repeat and Ig domain containing 1 (LINGO-1) [37, 38]. Further details are described in recent reviews [24, 39].



**Fig. (1).** The structural schema of p75NTR.

Schematic representation of full-length p75NTR and its short splice variant (s-p75NTR)

CRD: cysteine-rich domain

### SPLICING VARIANT

Although p75NTR is mainly expressed as a 75 kDa transmembrane glycoprotein, there is a protein isoform of p75NTR that arises from alternative splicing of exon III (Fig. 1). This isoform is left intact in a *p75NTR* mutant mouse line generated by Lee *et al.* [40,

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41]. In its extracellular domain, the short p75NTR variant (s-p75NTR) differs from the full-length p75NTR protein by the absence of three (CRD2, CRD3, and CRD4) of the four CRDs [42]. Neurotrophins bind to CRD2, CRD3 and CRD4 of p75NTR [15, 43]. Indeed, in HEK293 cells expressing recombinant s-p75NTR, the receptor did not bind to any neurotrophin [40]. Reverse transcription-polymerase chain reaction (RT-PCR) analysis performed on mouse, rat and human cells revealed that s-p75NTR is evolutionarily conserved and coexpressed with full-length p75NTR transcript at different embryonic stages, generally at substantially lower levels. Although the functions of s-p75NTR are largely unknown, some studies suggest that it is a functional molecule *in vivo*. s-p75NTR binds to RVG through CRD1, in contrast to requiring the other three CRDs for neurotrophin binding [36, 44]. Recently, a mammalian homologue of p75NTR, neurotrophin receptor homologue 2 (NRH2), was identified [45-47]. NRH2 contains transmembrane and cytoplasmic domains homologous to those of s-p75NTR; however, it lacks all of the CRDs [45]. NRH2 can interact with p75NTR and Trks, and mediate death or promote survival signals [46, 48].

### KNOCKOUT MICE

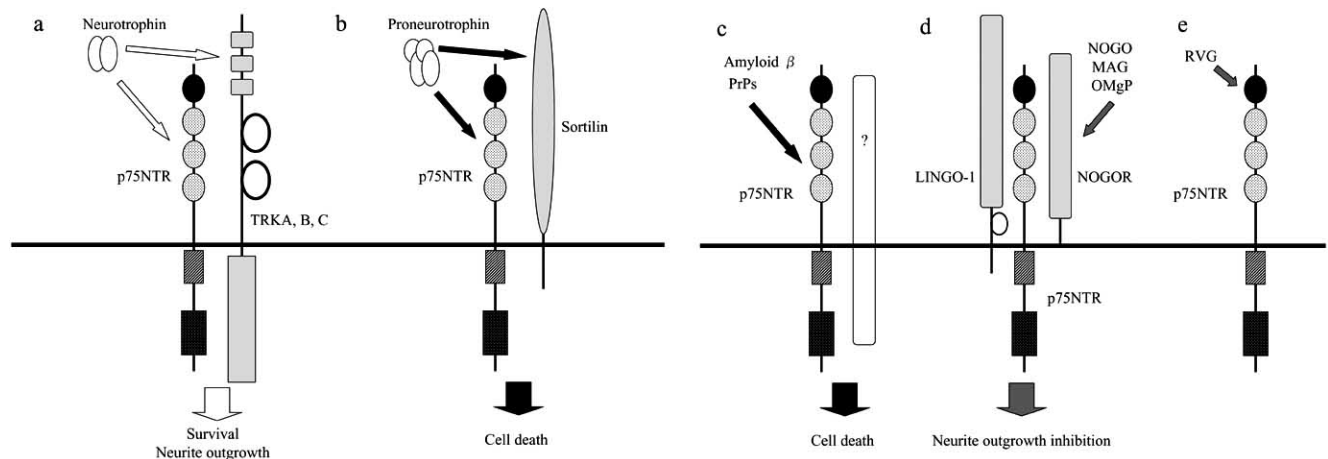
Lee *et al.* [41] generated mice lacking functional p75NTR by targeted disruption of exon III, which encodes CRD2, CRD3 and CRD4 (designated henceforth p75NTR<sup>exonIII-/-</sup>). p75NTR<sup>exonIII-/-</sup> mice were reported to be viable and fertile, and to develop deficits in heat sensitivity and skin defects in all extremities [41]. Immunohistochemistry revealed a lack of peripheral sensory nerve fibers expressing calcitonin-related peptide alpha (CALCA) and substance P [41]. Neonatal sympathetic and embryonic sensory neurons derived from p75NTR<sup>exonIII-/-</sup> mice showed reduced sensitivity to NGF and displayed deficits in developmental and injury-induced apoptosis [49, 50].

Because both the s-p75NTR transcript and its encoded protein are expressed in p75NTR<sup>exonIII-/-</sup> mice, von Schack *et al.* [40] targeted exon IV to generate a null mutation (designated henceforth p75NTR<sup>exonIV-/-</sup>). In both p75NTR<sup>exonIII-/-</sup> and p75NTR<sup>exonIV-/-</sup> mutants, alterations in cholinergic neurons in the basal forebrain, hippocam-

pal neurons, and neurogenic precursor cells in the subventricular zone (SVZ) have been observed (Table 1) [40, 41, 49-74]. p75NTR<sup>exonIV-/-</sup> mice display more severe phenotypes than p75NTR<sup>exonIII-/-</sup> mice, particularly in the nervous systems. p75NTR<sup>exonIV-/-</sup> mice displayed a larger reduction in the number of dorsal root ganglia (DRG) neurons and Schwann cells, partial perinatal lethality, and defects in the vascular system that have not been observed in p75NTR<sup>exonIII-/-</sup> mice [40].

Alzheimer's disease, which causes deficits in learning and memory processes, is accompanied by a loss of cholinergic function [75-77]. Some studies have indicated an increase in the number of cholinergic forebrain neurons in p75NTR<sup>exonIII-/-</sup> mice [53, 54, 78], while others reported a decrease [67] or no significant change in the numbers of such neurons [52]. To resolve these conflicting results, Naumann *et al.* analyzed the numbers of cholinergic neurons in the medial septal nucleus of p75NTR<sup>exonIII-/-</sup> and p75NTR<sup>exonIV-/-</sup> mice on a Sv129/BALB/c genetic background and a back-crossed congeneric strain (C57BL/6). The p75NTR<sup>exonIII-/-</sup> mutation led to a moderate increase (+13%) in the number of cholinergic neurons only after back-crossing onto a C57BL/6 background. Interestingly, s-p75NTR was present at substantially higher levels in mice with the Sv129 background compared with C57BL/6 mice, which might help to explain this result. In contrast to the p75NTR<sup>exonIII-/-</sup> mutation, the p75NTR<sup>exonIV-/-</sup> mutation resulted in an over 20% increase in the number of cholinergic neurons, independent of genetic background. They concluded that p75NTR<sup>exonIV-/-</sup> mutation increases the number of cholinergic neurons in the medial septum [54].

The p75NTR<sup>exonIV-/-</sup> mutation results in severe ataxia in mice and precludes detailed behavioral testing [40]. When spatial learning was examined in p75NTR<sup>exonIII-/-</sup> mice, conflicting results were observed, depending on test paradigms. Peterson *et al.*, who found a markedly reduced number of cholinergic septal neurons, reported deficits in acquisition of the Morris water maze, inhibitory avoidance, and habituation tasks in adult p75NTR<sup>exonIII-/-</sup> mice [64]. Such deficits in p75NTR<sup>exonIII-/-</sup> mice in the Morris water maze were subsequently supported by Wright *et al.* [66]. Performance in the Barnes maze, by contrast, was superior in p75NTR<sup>exonIII-/-</sup> mice than in control mice [52]. The Barnes maze is a dry version of the circu-



**Fig. (2).** p75NTR is involved in different biological activities, depending on its different ligands and co-receptors.

- p75NTR physically interacts with TRK receptors (TRKA, TRKB, and TRKC) and enhances their abilities to respond to neurotrophins.
- Interaction of p75NTR with sortilin mediates proapoptotic signals in response to proneurotrophin binding.
- Amyloid beta binds to p75NTR and promotes cell death.
- p75NTR forms a complex with NOGOR that results in growth inhibitory signals to be transduced in response to NOGO, myelin-associated glycoprotein (MAG), or oligodendrocyte myelin-glycoprotein (OMgP).
- RGV binding occurs on CRD1, although this binding is not essential for RV infection.

**Table 1. Neuronal and Behavioral Phenotypes of *p75NTR* Knockout Mice**

Year	Authors	Region	KO	Phenotypes
1992	Lee, KF et al.[41]	SN	III	Marked decrease in sensory innervation by calcitonin gene-related peptide- and substance P-immunoreactive fibers and loss of heat sensitivity
1993	Davies, AM et al.[49]	TSN	III	Altered response to NGF in trigeminal sensory neurons
1994	Lee, KF et al. [50]	DRG, SCG	III	Excessive loss of DRG and SCG neurons <i>in vivo</i>
1995	Curtis, R. et al. [70]	DRG	III	Retrograde axonal transport of NT-4 and BDNF, but not NGF, was dramatically reduced
1997	Yeo, TT et al. [53]	BFCN	III	Increase in the number, size, activity, and target innervation of BFCNs
1997	Peterson, DA et al. [67]	BFCN	III	Decrease in the number of BFCNs
1997	Bergmann, I. et al.[72]	Cutaneous SN	III	Reduction of the epidermal innervation density
1998	Banji, SX et al. [55]	SCG	III	Sympathetic neuron death was developmentally delayed
1998	Ferri, CC et al. [57]	Facial MN	III	Significant improvement of survival in the adult KO mice, compared to WT, following injury
1999	Brennan, C. et al. [65]	SCG	III	In <i>p75NTR<sup>-/-</sup> NGF<sup>+/-</sup></i> mice, SCG neuron number was restored to WT levels. ( <i>NGF<sup>+/-</sup></i> mice had 50% fewer SCG neurons.)
1999	Peterson, DA et al. [64]	BFCN	III	Impairments in several learning and memory tasks, such as Morris water maze, inhibitory avoidance, motor activity, and habituation tasks
1999	Yamashita, T. et al. [71]	SN, MN	III	Reduced outgrowth of sensory and motor axons
1999	Frade, JM et al. [56]	Retina, Spinal cord	III	In <i>p75NTR<sup>-/-</sup></i> embryos, cell death was reduced in the retina and in the spinal cord
2000	Bentley, CA et al. [51]	DRG	III	Abnormalities of axon growth, arborization, and Schwann cell migration during development
2000	Greferath, U. et al. [52]	BFCN	III	Increase in the number of BFCNs, marked increase of the size of BFCNs, and better spatial learning performance
2000	Coulson, EJ et al. [69]	DRG	III	Resistance for cell death after withdrawal from cultured medium
2001	von Schack et al. [40]	DRG	IV	Larger reduction in the number of DRG neurons and Schwann cells
2002	Naumann, T. et al. [54]	BFCN	III, IV	Increase in the number of BFCNs (medial septum), compared with controls
2002	Troy, CM et al. [58]	HN	III	Marked reduction in the number of dying neurons after induced seizures
2004	Wright, JW et al. [66]	(Behavior)	III	Impairments in Morris water maze task
2005	Zagrebelky, M. et al. [59]	HN	III, IV	Postnatal hippocampal pyramidal cells in both mutant lines had a higher spine density and greater dendritic complexity than WT mice
2005	Rosch, H. et al. [60]	HN	III, IV	Hippocampal LTD was impaired in both <i>p75NTR</i> -deficient strains
2005	Woo, NH et al. [61]	HN	III	Impairment of the NMDA receptor-dependent LTD and a decrease in the expression of <i>NR2B</i>
2005	Scott, ALM et al.[73]	Spinal cord	III	In rhizotomy-treated <i>p75NTR<sup>-/-</sup></i> mice, intraspinal sprouting was significantly augmented
2006	Sato, T et al. [62]	SGN, HCs	III	Progressive hearing loss, degeneration of SGNs, and severe loss of HCs
2006	Volosin, M. et al. [68]	BFCN	III	65% decrease in the number of dying neurons in the medial septum and 80% decrease in the diagonal band compared with the WT mice 1day after kainic acid treatment
2007	Young, KM et al. [63]	NPC in SVZ	III	70% reduction in neurogenic potential <i>in vitro</i> , significant reductions of numbers of PSA-NCAM positive SVZ neuroblasts <i>in vivo</i> , and a lower OB weight
2007	Jansen, P. et al.[74]	SCG	III	Significant increase in the number of sympathetic neurons and protection against age-associated cell death

In the KO column, III and IV represent *p75NTR<sup>exon III</sup>* and *p75NTR<sup>exon IV</sup>*, respectively. BFCN: Basal forebrain cholinergic neuron, CNS: Central nervous system, DRG: Dorsal root ganglia, HC: Ear hair cell, HN: Hippocampal neurons, LTD: Long-term depression, MN: Motor neuron, NMDA: N-methyl-D-aspartate, NPC: Neurogenic precursor cells, NR2B: N-methyl-D-aspartate receptor 2B, OB: Olfactory bulb, PSA-NCAM: Polysialic acid neural cell adhesion molecule, SCG: Superior cervical ganglion, SGN: Spiral ganglion neuron, SN: Sensory neuron, SVZ: Subventricular zone, TSN: Trigeminal sensory neuron, WT: Wild-type.

lar water maze that provides a spatial cue to permit navigation to a safe location. Unlike the study of Peterson *et al.* [64, 67], Greferath *et al.* [52] did not find a markedly reduced number of cholinergic septal neurons, and reported that cholinergic cells in *p75NTR<sup>exonIII/-</sup>* mice were significantly larger than those in control mice in the medial septal area and in the diagonal band of Broca. They discussed that the improved performance of *p75NTR<sup>exonIII/-</sup>* mice in the Barnes maze correlates with their hypertrophied cholinergic neurons. Taken together, these findings suggest that *p75NTR* may act as a negative regulator of cholinergic neurons in the forebrain.

### ***p75NTR* and Neurodegenerative Disease**

Alzheimer's disease is pathologically characterized by extensive neuronal cell death, synaptic loss, intracellular neurofibrillary tangles, and extracellular senile plaques and, as described above, is

associated with a loss of cholinergic neurons resulting in profound memory disturbances and irreversible impairment of cognitive function [75-77, 79-81]. In the postmortem brains of patients with Alzheimer's disease, the levels of proneurotrophins, which bind to *p75NTR* and promote neuronal death, have been found to be increased in several studies [82-86]. In cellular models of neurodegenerative diseases, up-regulation and ligand activation of *p75NTR* have been shown to mediate neuronal cell death [31, 32, 69]. Sortilin, a member of the vacuolar protein sorting 10 protein (Vps10p) domain receptor family, was shown to form a receptor complex with *p75NTR* as an essential component for transmitting proneurotrophin-dependent cell death signals [31, 32]. Sortilin KO (*Sort1<sup>-/-</sup>*) mice were shown to be resistant to age-dependent degeneration of sympathetic neurons [74]. In *p75NTR<sup>exonIII/-</sup>* mice, protection against age-associated cell death was also observed, supporting the possibility of a functional interaction between *p75NTR* and

sortilin in this process [74]. Of note, amyloid beta peptides, the major constituents of senile plaques, have been characterized as ligands for p75NTR [33, 87, 88]. Although this signaling *in vivo* is still unclear, a number of reports have suggested that p75NTR is involved in the promotion of cell death signaling by amyloid beta peptides *in vitro* [89-95]. A recent study provided evidence of a direct link between p75NTR signaling and amyloid beta-induced toxicity in hippocampal neurons *in vitro* and in cholinergic basal forebrain neurons *in vivo* [88]. Both proneurotrophin- and amyloid beta-regulated signaling pathways involving p75NTR *in vivo* seem promising in order to understand the etiology of Alzheimer's disease and to develop novel therapeutic drugs.

### p75NTR in Neuropsychiatric Diseases

A number of studies indicate that neurotrophins also play an important role in neuropsychiatric diseases such as depression and schizophrenia (reviewed in [7-13, 96]). Therefore, p75NTR, as a pan neurotrophin receptor, might play a key role in neuropsychiatric diseases. As the first study examining a possible association between p75NTR and psychiatric diseases, we reported that a missense polymorphism (S205L) in p75NTR was associated with depressive disorder and attempted suicide in a Japanese population [97]. The frequency of mutant-type (L205) was significantly decreased in patients compared with controls ( $P < 0.05$ , odds ratio 0.54, 95% CI 0.31-0.94), suggesting that this variant may have a protective effect against the development of major depression. Furthermore, this association was more strongly observed in patients with a history of attempted suicide than in those without such a history. A recent study in a North American population, however, failed to obtain evidence for an association between p75NTR polymorphisms, including S205L, and a risk of childhood-onset mood disorder (COMD) or suicide attempt in COMD [98]. In order to clarify the relationship between p75NTR and depressive disorder and suicidal behavior, further studies in large samples are required.

Many lines of evidence indicate that early neurodevelopmental abnormalities contribute to the pathogenesis of schizophrenia [99-101]. Schizophrenia is also characterized by adult-onset subcortical dopaminergic hyperactivity (see, for example, [102, 103]) and disrupted prepulse inhibition (PPI) of acoustic startle (see, for example, [104-107]). p75NTR is widely expressed in the developing central and peripheral nervous systems during the period of synaptogenesis and developmental cell death [108]. Rats treated with neonatal injections of p75NTR antibody conjugated to saporin into the developing prefrontal cortex showed impaired PPI and behavioral changes characteristic of adult-onset dopaminergic hyperresponsivity [109]. It has been suggested that prenatal vitamin D3 depletion can lead to changes in many features of brain development, including morphology, cellular proliferation and neurotrophin systems, which suggests a potential risk-modifying factor for schizophrenia. Interestingly, this change induced by vitamin D3 depletion includes a marked decrease in the expression of p75NTR, and vitamin D3-responsive elements are present in the promoter region of p75NTR [110]. Recently, the early growth response (Egr) transcriptional regulators, Egr1 and Egr3, were identified as direct modulators of p75NTR expression [111]. Egr1 and Egr3 bind to and transactivate the p75NTR promoter *in vitro* and *in vivo* [111]. EGR3 was identified as a potential susceptibility gene in schizophrenia by a recent genetic association study and postmortem brain analysis [112].

Numerous studies have found subregional abnormalities of the brain in patients with schizophrenia, including smaller hippocampal volume, larger ventricles, smaller cerebral volume, reversed asymmetry in the superior temporal gyrus, and smaller volume of the medial temporal lobes (reviewed in [113-115]), and in those with major depression, including reduced volumes of hippocampus, amygdala and anterior cingulate (reviewed in [113, 116, 117]).

There are several lines of evidence suggesting alterations of oligodendrocytes in schizophrenia, for example, lowered density of oligodendroglia [118, 119]. Possibly pertinent to this, proneurotrophins induce death of oligodendrocytes expressing p75NTR [31]. Taken together, these findings suggest that p75NTR might play an important role as a key molecule in such volume changes of the brain in patients with neuropsychiatric diseases.

### DRUG CANDIDATES

Agonists or antagonists for p75NTR would contain structural determinants of one or more neurotrophin active sites that interact with p75NTR. Longo *et al.* [120] revealed that a peptide corresponding to the region between amino acid residues 28 and 38 of NGF inhibits its neurotrophic effects on DRG neurons. Subsequently, short synthetic peptides corresponding to the beta-hairpin loop of NGF were designed, blocking neuronal death in culture [121]. This NGF-inhibitory activity was p75NTR dependent, requiring both peptide cyclization and dimerization [121]. Turner *et al.* [122] showed that application of a cyclic decapeptide p75NTR antagonist, containing amyloid beta residues 28-30 (Lys-Gly-Ala), protects against NGF-induced death signaling in cultured NSC-34 cells.

Recently, Massa *et al.* [123] identified several small molecules as novel ligands of p75NTR, including a derivative of caffeine, LM11A-24. These compounds are non-peptidyl mimetics of the neurotrophin loop 1 domain identified by tandem *in silico* and *in vitro* screening. LM11A-24 bound to p75NTR, exerted potent neuroprotective effects through one or more p75NTR-dependent mechanisms, and stimulated survival pathways in hippocampal neurons. It also prevented p75NTR-dependent apoptosis induced by proNGF in oligodendrocytes [123]. Subsequently, Pehar *et al.* [124] showed that LM11A-24 was able to inhibit p75NTR-dependent motor neuron death induced by NGF. Intriguingly, the apparent potency of LM11A-24 was considerably higher than that of the above-mentioned peptide-based antagonist containing amyloid beta residues 28-30 (Lys-Gly-Ala) in motor neuron-like NSC-34 cells [123, 122]. LM11A-24 and its related derivatives capable of crossing the blood-brain barrier are expected to become leading candidates in the development of therapeutic strategies targeting p75NTR.

### CONCLUSION

We focused on recent findings concerning p75NTR in relation to neuronal function, its possible relevance to neuropsychiatric diseases, and progress in genome-based drug discovery targeting p75NTR. p75NTR associates with many kinds of co-receptors and ligands, and transduces various signals, which complicate the understanding of the role of p75NTR *in vivo*. However, in p75NTR KO mice, an increase in the number and size of cholinergic neurons in the medial septum and protection against age-associated neuronal cell death were observed, which raises the possibility that p75NTR might regulate cholinergic neurons negatively in the forebrain. p75NTR, as a mediator of death signaling in both neurons and oligodendrocytes, might contribute to the morphological changes in the brain and subsequent development of neuropsychiatric diseases. Thus, suppression of p75NTR might be a possible therapeutic strategy. Recently, virtual screening *in silico* has been put to practical use in drug discovery and some small molecule ligands for p75NTR have been identified (for example, LM11A-24). Studies on such small ligands for p75NTR with respect to their therapeutic and protective effects in neuropsychiatric diseases are warranted.

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