# Abeta and the neurotrophin receptor p75

## A possible physiological role of Abeta as a crosslinker

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Amyloidopathic degenerative diseases such as Alzheimer's disease, Parkinson's disease, prion diseases and type 2 diabetes mellitus are suspected of having deleterious mechanisms in common, and in this context oligomers of the disease-related amyloidogenic proteins have become the focus of attention. For instance, Abeta oligomers can impair synaptic function and morphology and may cause defects of the cell membrane. The supposed detrimental role of amyloid aggregates species has led to therapeutical approaches aiming at the reduction or elimination of Abeta aggregates, without real success to date. This failure indicates that more research into the natural functions of Abeta is needed. It has to be taken into account that Abeta oligomers may have a physiological role and that only overproduction and/or conformational change of Abeta might render them pathogenic, as postulated by some researchers; indeed, recent reports indicate physiological functions of Abeta at synapses (e.g. Puzzo et al., 2008; Abramov et al., 2009). The following "Abeta-crosslinker-hypothesis" describes a possible natural function of Abeta oligomers and a link between this function and pathogenic effects of amyloid aggregate species.

**Abeta can crosslink p75 with various proteins and mediate a direct cooperation between the receptor and these proteins.**

According to this concept, the amyloidogenic nature of Abeta facilitates the direct cooperation of a vital neuronal signaling system, the neurotrophin system, with other synapse-modulating proteins and thus optimizes neuronal connectivity and activity. Development, maturation and function of nerve cells are influenced by external signaling molecules that bind to cell surface receptors and activate them. The neurotrophins regulate (among other cellular activities) the outgrowth of nerve cell processes (neurites) and the formation and function of synapses. They bind to two types of receptors, the Trk receptors with three relatively neurotrophin-specific subtypes and the p75 receptor, which binds all neurotrophins. These receptors are surface proteins with an extracellular, a transmembrane and an intracellular domain; the extracellular domain encompasses a complex binding site for the neurotrophins, and in the case of p75 an unstructured stalk domain that connects this binding site with the transmembrane domain. Neurotrophins bind to their receptors as dimers that couple two receptors of the same type or perhaps bind to pre-formed receptor dimers, alter their conformation and initiate processes in the specialized surroundings (membrane rafts) of the receptors that lead to the clustering of a number of receptors; such clusters may also contain Trk-p75 complexes. The triggered intracellular signaling cascades of the Trk receptors are essentially neurotrophic and support vital cell functions and synaptic activity while the p75 receptor can have both neurotrophic and inhibitory or pruning effects. This somewhat paradox behavior and the existence of co-receptors of p75 have led to the idea that the functions of p75 are partly the result of cooperations of p75 with other receptors. Trk and p75 receptors represent a kind of dual growth and function control, with p75 balancing the Trk effects and optimizing the morphological and functional integration of neurons into their cellular context. Under certain circumstances, e.g. when a cell is overstimulated with a neurotrophin, p75 can trigger programmed cell death; therefore and because of its structural similarity to other apoptotic receptors, it is also regarded as a death receptor. Apart from neurotrophins, aggregated Abeta, too, can associate with the neurotrophin-binding site of p75 and induce apoptosis. Evidence presented in the full text of the hypothesis (see also comment on Knowles et al., 2009) shows that in addition to this "upper binding site" there is a second binding site for Abeta on p75 that starts within the stalk domain and possibly extends into the transmembrane domain of p75. This "stalk binding site", which has been overlooked in earlier investigations and which probably binds Abeta monomers with high affinity, serves as the basis for the present hypothesis.

Abeta monomers are produced by cleavage of the receptor-like amyloid precursor protein APP and in their unbound state can be anchored in membranes (especially the cell membrane) or be in solution. Like the p75 stalk binding site for Abeta, the amino acid sequence of Abeta within surface APP starts in the extracellular juxtamembrane region and extends into the transmembrane domain. It has been shown that aggregated Abeta can associate with it, and one may assume that membrane-anchored Abeta monomers or oligomers can do the same. Considering the similar membrane-associated positions of the stalk binding site within p75 and the homologous sequence of Abeta within APP, the likely binding of Abeta monomers (or oligomers) to these two sites and the natural propensity of Abeta for aggregation, the idea suggests itself that p75 and APP may be crosslinked by a short membrane-anchored Abeta oligomer. Such crosslinking would arrange the two proteins in a way that - upon ligand-induced p75 activation - facilitates an interaction of their intracellular domains and ultimately their functional cooperation; an independent recent publication indeed reports that p75 and APP can interact (see comment on Fombonne et al., 2009). The formation of an Abeta link should be supported by GM1 gangliosides that are present in certain membrane rafts and that can bind soluble or membrane-anchored Abeta and catalyze its oligomerization; the membrane raft would also determine the length of a crosslinking oligomer. Abeta links between p75 and APP might form upon p75 activation or prior to it and in the latter case accelerate p75-APP interaction upon stimulation. p75 should also cooperate with certain transmembrane C-terminal fragments of APP (such as C99, cf. Fombonne et al., 2009), which have been reported to be more common than full-length APP at normal APP expression (see comment on Muresan et al, 2009). Hints in the literature indicate that a cooperation of p75 and APP should be neurotrophic and promote cell survival**.** As p75-Abeta-APP complexes are eventually degraded, the cooperation between p75 and APP consumes Abeta, and this may be one reason for the upregulation of Abeta production by p75. In contrast, the Trk receptor TrkA inhibits Abeta production. In Alzheimer's disease and frequently also in normal age, TrkA expression (but not p75 expression) is diminished in certain brain areas and with it the inhibitory effect of TrkA on Abeta production; the elevated ratio p75/TrkA may then significantly contribute to Abeta overproduction and accumulation. Abeta links should not be formed between the stalk binding sites of two p75 molecules as such links would compete with the neurotrophic cooperations between p75 and APP and reduce them and/or cause constitutive activation of p75. Biochemically, this may be guaranteed by an asymmetry in the binding sites of non-beta-sheet Abeta molecules for other Abeta molecules and for the stalk binding site of p75: the far end of an Abeta link growing from one p75 receptor should not dock to the stalk binding site of another p75 receptor or to an Abeta associated with this site because it presents the wrong side. As on the other hand Abeta oligomers are indeed able to stimulate the p75 receptor, it must be the upper binding site for Abeta on p75 that mediates this activation. Therefore the two binding sites for Abeta on p75 have different physiological functions: the stalk binding site makes p75-APP cooperations possible, and the upper binding site serves the activation of p75 by certain Abeta aggregate species which should be regarded as regular ligands of p75 and which may e.g. help to protect neurons from overexcitation by inducing postsynaptic depression through p75. If there are not too many aggregates with beta-sheet conformation (see further below), p75 activation via the upper binding site permits Abeta-mediated neurotrophic and neuroprotective cooperations of p75 and leads (by a negative feedback mechanism) to an increased consumption of Abeta; a cytoprotective effect of Abeta-stimulated p75 against Abeta toxicity was indeed observed by several research groups. The elevation of p75 and APP expression and Abeta production observed upon brain traumata indicates that Abeta oligomers can complement neurotrophins or substitute for them and support neuronal regeneration via p75.

The presented cooperation hypothesis is fully consistent with the scientific literature which provides many hints that p75 and APP work hand in hand during neurite and synapse formation and in synaptic function, and that APP and the neurotrophic cleavage product of APP, sAPPalpha, substantially contribute to certain neurotrophin effects; these hints have been collected in the detailed text of the hypothesis. Apart from APP, alpha-synuclein and the prion protein PrPc, too, influence the synapse, can interact with Abeta and - according to the hypothesis - are able to cooperate with p75 through Abeta oligomers and to enhance the neurotrophic and neuroprotective functions of the receptor; such cooperation could for instance underlie the neuroprotective effect of p75 against Abeta. The recently shown binding site of PrPc for Abeta (see comment on Lauren et al., 2009) and the demonstrated interaction of p75 and APP (Fombonne et al., 2009) are consistent with the hypothesis. Further potential cooperation partners of p75 with binding sites for Abeta and synaptic functions include the nicotinic acetylcholine receptor alpha7 and the metabotropic glutamate receptor mGluR5. Renner et al. (2010; see comment) demonstrated that administrated Abeta oligomers draw mGluR5 receptors into the synapse, cluster them and cause synaptotoxic effects just like chemical crosslinking of mGluR5; this strongly hints at direct or indirect Abeta-mediated crosslinking. In this clustering process, Abeta might also connect mGluR5 with p75 and (indirectly) with NMDAR; the latter two receptors are core elements of the glutamatergic postsynaptic density and can be linked by PSD-95 (Sandoval et al., 2007). Abeta-mediated crosslinking may even regulate the supposedly direct association of Trk receptors with p75. Zampieri and Chao (2006) thought that the association of p75 with TrkA might be mediated by sequences in the stalk domain of p75 and that these sequences "might also play a pivotal role in controlling the association of p75 with its co-receptor partners". Matrone et al. (2009)

reported that an increase in endogenous Abeta (triggered by NGF withdrawal) can induce association of TrkA with p75, transactivation of TrkA by p75, and proapoptotic signaling of TrkA; suitable antibodies against Abeta prevent these effects. A crosslinking of p75 and TrkA by Abeta would signify that Abeta could substantially modulate neurotrophin receptor signaling and affect many cellular processes; such crosslinking, however, would also sensitize the neurotrophin receptor system to excess Abeta. For details click here or download the file TrkA-Abeta-p75.pdf.

The postulated Abeta-mediated cooperation of p75 with proteins such as APP, PrPc and alpha-synuclein regulates synaptic and other functions of these proteins through neurotrophin and Abeta signals and provides a number of cell-biological advantages, in particular the synchronization and coordination of these functions, the reduction of regulation and energy costs, the acceleration of time-critical processes and altogether a simpler and more robust implementation of complex tasks such as synapse formation. Accordingly, the Abeta oligomers mediating this cooperation may have a physiological function that depends on the amyloidogenic nature of Abeta. Current therapeutical approaches aiming at their elimination or neutralization (e.g. by active immunization against Abeta oligomers) might conflict with this physiological role and in the long term impair the functionality of the brain.

A shortened isoform of p75, s-p75, has been reported to be coexpressed with full-length p75 and to be also expressed in certain strains of p75-deficient mice; s-p75 lacks the cysteine-rich domains 2-4 that encompass the neurotrophin binding site and (probably) the upper binding site for Abeta. Significant levels of s-p75 (and a marked increase of full-length p75) have been observed in sciatic nerve protein of a SOD1(G93A) ALS mouse model during endstage disease (Turner et al., 2009), which might explain why knockout of p75 ExonIII, which permits expression of s-p75, essentially does not affect ALS onset and progression in ALS mouse models (Küst et al., 2003) while antisense peptide nucleic acid-mediated knockdown of p75 does (Turner et al., 2003; see also comment on Reyes et al., 2010). Due to the lack of the neurotrophin binding site, s-p75 cannot be activated by neurotrophins and probably has no upper binding site for Abeta since this binding site overlaps the neurotrophin binding site; however, crosslinked s-p75 might be activated by activated potential binding partners such as dimerized prion. Since s-p75 contains the stalk binding site of p75 for Abeta it could be activated by beta-sheet Abeta (or beta-sheet aggregates of other amyloidogenic proteins that interact with Abeta or the stalk binding site of p75, see next paragraph). By competing with p75 for Abeta aggregates and thus protecting the p75 stalk against beta-sheet Abeta, s-p75 would support Abeta-mediated neurotrophic cooperations of full-length p75. Due to the distinctly lesser expression of s-p75, its signaling should be secondary to p75 signaling and therefore support neuroprotective p75 signaling up to a certain threshold concentration of Abeta aggregates. At higher concentrations of Abeta, when the stalk binding site of full-length p75, too, is bound by aggregated Abeta (see next paragraph) and Abeta-mediated neurotrophic cooperations of p75 are largely prevented, s-p75 might accelerate Abeta-induced cell death via p75. s-p75 has apoptotic potential since even a truncated form of s-p75 with shortened stalk binding site of Abeta (detected in mice expressing a mutated p75 gene with deleted ExonIV) showed apoptotic activity when it was overexpressed in the absence of wildtype p75. Physiologically, s-p75 might serve as a secondary receptor that has beta-sheet aggregates of Abeta as activating ligands and that enhances or amplifies effects of p75-Abeta interaction, in particular neuroprotection against Abeta (see comment on Bengoechea et al., 2009); crosslinked s-p75 might also be activated by certain binding partners and support and complement the signaling of these partners.

**Beta-sheet aggregates of certain amyloidogenic proteins can hijack the p75 stalk binding site for Abeta and cause detrimental effects of the receptor by activating p75 and by preventing its neurotrophic cooperations.**

According to many reports, higher concentrations of aggregated Abeta can cause the formation of excess and aberrant neuronal connections, the weakening and elimination of synapses and eventually cell death. Experiments with cell cultures and living animals attribute a crucial role in Abeta-mediated degeneration to the receptor p75. For instance, the injection of aggregated Abeta into a certain brain area of a mouse with normal expression of p75 led to degenerative effects that were not seen in a p75 knockout mouse (Sotthibundhu et al., 2008). In contrast, aggregated Abeta in concentrations below a certain threshold enhances the neuroprotective functions of p75; this threshold rises with p75 expression. An explanation for this may be that though the neuroprotective cooperations of p75 are normally induced or activated by neurotrophin stimulation of p75 they can also be activated by Abeta aggregates that bind to the upper binding site of p75. Continued overstimulation of the receptor by Abeta aggregates, however, produces critical levels of ceramide and oxygen radicals, augments the inhibitory and pruning effects of p75, increases apoptotic signaling and further upregulates Abeta

production; it may also contribute to intracellular accumulation of aggregated Abeta through internalization of activated p75. In addition to overstimulation of p75, an excess of beta-sheet aggregates of Abeta can prevent the neuroprotective cooperations of the receptor. Abeta monomers within beta-sheet aggregates have - apart from the first 16 amino acids and a hinge region around amino acid 29 - a planar conformation with extensive interdigitation of amino acid side chains of neighboring Abeta molecules, and form stable stacks of parallel in-register beta-sheets; stacked Abeta monomers can still bind to the p75 receptor or to p75-associated Abeta monomers. Long-term overproduction of Abeta can produce enough beta-sheet aggregates to block the stalk binding site of p75 receptors and also p75 stalk-associated Abeta monomers and thus prevent the formation of Abeta links between p75 and its cooperation partners. Besides, such aggregates are able to activate and cluster p75 receptors not only via the upper binding site but also via the stalk binding site, in contrast with non-beta-sheet Abeta oligomers. If beta-sheet aggregates of other amyloidogenic proteins can directly interact with p75 or with p75 stalk-associated Abeta, then they too shall cause unphysiological p75 activation, prevent neurotrophic p75 cooperations and damage the cells. Since Abeta can interact with aggregates of prion protein, alpha-synuclein, superoxide dismutase 1 (Yoon et al., 2009) and amylin, the described deleterious mechanism might play a significant role in Alzheimer's and Parkinson's disease, in prion diseases, in certain forms of amyotrophic lateral sclerosis (see comment on Reyes et al., 2010), in type 2 diabetes mellitus, and presumably in other degenerative diseases. This mechanism is induced when a natural function of Abeta monomers and short oligomers is hijacked by an excess of beta-sheet aggregates, and it has the consequence that the p75 receptor can act as a catalyst of certain neurodegenerative diseases.

**Suitable fragments of the p75 stalk binding site for Abeta can prevent p75-mediated cell damage by amyloid aggregates.**

Cultured neurons that express p75 and that are stimulated with higher concentrations of aggregated Abeta or NAC (an aggregating fragment from the central part of alpha-synuclein) die in considerable numbers, but there is no significant cell death when the same cultures are incubated with certain fragments of the stalk binding site of p75 and then stimulated as described; presumably, the amyloid aggregates are neutralized by the fragments. Interestingly, the proteolysis of p75 that prevents further ligand-induced p75 signaling, produces a fragment of the stalk binding site of p75 with unknown function that might protect the stalk binding site of intact p75 receptors from toxic amyloid aggregates; if this fragment has indeed such a protective function then it should have been honed by evolution, which might make it or fragments of it useful for therapeutic application. Since the examined stalk fragments probably do not impair natural p75-mediated neurotrophin effects (tested for the activation of Ras and for short-term neurite outgrowth) it may be assumed that they do not prevent the cooperation of p75 with its partners. The lack of a secondary structure of the p75 stalk also raises the hope that the fragments (like the stalk) do not evoke an immune response. These arguments suggest that fragments (or suitable derivatives) of the stalk binding site should be taken into consideration as potential natural drugs for Alzheimer's disease and other neurodegenerative diseases. In the best case, several such diseases might be treated with one single drug. The therapeutical approach may be used freely as it has not been patented.

**Summary**

In brief, the hypothesis says that Abeta can crosslink the receptor p75 and various proteins and mediate their functional cooperation, that the stalk binding site of Abeta on p75 is crucial to this process and that it can be hijacked by beta-sheet aggregates of certain amyloidogenic proteins. If such aggregates can interact with Abeta they should be able to cause neuronal damage and cell death via p75. When in the course of a neurodegenerative disease inflammation ensues (which upregulates p75) then the receptor can cause additional damage and death due to overstimulation of neurons with the nerve growth factor NGF that - induced by amyloid aggregates - is secreted from astrocytes. In these ways the p75 receptor can accelerate the progress of certain neurodegenerative diseases and aggravate their effects. The prevention of amyloid-induced and p75-mediated damage e.g. by means of derivatives of the stalk binding site of p75 might enable the organism to slow or stop the progress of such a disease.

From a cell-biological perspective, Abeta-mediated crosslinking (like certain scaffold proteins) can be regarded as a means of receptor networking that permits interconnection of signaling processes and modulation of neurotrophin receptor signaling and thus influences many aspects of cell life.

*PDF files*

**Abeta-crosslinker-hypothesis**  (abeta-p75.pdf, 1.4 MB; original text, 25 September 2008)

**Abeta may also crosslink TrkA and p75**  (TrkA-Abeta-p75.pdf; 7 February 2010)

**This webpage as PDF**  (Abeta-p75-overview.pdf)

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*Comment: Bengoechea et al. report that aggregated Abeta reduces neurite outgrowth from p75-deficient sympathetic neurons, and that p75-deficient J9 AD mice show severe sympathetic innervation defects which can be partially prevented by elimination of one allele of BACE1. They conclude that p75 can protect the sympathetic nervous system from adverse effects of Abeta, in agreement with earlier reports on a neuroprotective effect of p75 against Abeta (Zhang et al., 2003; Costantini et al., 2005).*

*According to reports by von Schack et al. (2001) and Naumann et al. (2002), the p75 knockout mouse used in the study (Lee et al., 1992; p75ExonIII-/- mouse) may produce a truncated p75 protein (s-p75) that was also observed in certain mouse strains with wildtype p75. s-p75 lacks the neurotrophin binding site and includes the cysteine-rich domain 1 and the stalk, transmembrane and intracellular domains of p75. Another p75 knockout mouse (p75 ExonIV-/- mouse) produces a truncated s-p75 protein (here designated ts-p75) that encompasses a small portion from the stalk and the entire transmembrane and intracellular domains of p75 (Paul et al., 2004); ts-p75 is membrane-associated and (when overexpressed) able to induce apoptotic signaling.*

*The existence of the truncated s-p75 isoform has been discussed controversially, which may have been caused by the use of different p75ExonIII-/- mouse strains. The careful study by Naumann et al. (2002) demonstrates that the level of s-p75 mRNA is strain dependent. Analysis by reverse transcription-PCR revealed that s-p75 mRNA in P15 whole brain and medial septum (MS) accumulates at much higher levels*

*in Sv129 mice than in C57BL/6 (B6) mice, in contrast with comparable levels of full-length p75 mRNA in both strains. Naumann et al. further observed that pure B6 animals at P15 have approximately 33% fewer cholinergic MS neurons than Sv129 animals, and that the number of these neurons is significantly elevated by 6.5% in the p75ExonIII-/- mouse with the original mixed Sv129/BALB/c background and by 13% in a corresponding congenic B6 mouse (relative to controls with wildtype p75). The authors interpreted the latter results to be due to the prevention of p75-mediated developmental cell death or/and to an increased efficiency of TrkA signaling. The fact that B6 mice with the p75ExonIV mutation, which prevents the expression of wildtype p75 and s-p75, have a substantially higher increase in the number of cholinergic MS neurons than B6 mice with the p75ExonIII mutation (28%:13%; Naumann et al.) indicates a negative influence of s-p75 on the number of these neurons in B6 p75ExonIII-/- mice; Naumann et al. supposed that "s-p75 partially compensates for the lack" of full-length p75. That B6 p75ExonIV-/- mice also express an isoform of p75 (which is a truncated s-p75; Paul et al., 2004) should not devalue this inference since this isoform is pro-apoptotic and - if s-p75 were non-apoptotic - should rather diminish the increase in cholinergic MS neurons than enlarge it; the pro-apoptotic property of the truncated s-p75 (Paul et al.) might even imply a similar (and perhaps stronger) function of s-p75. As a consequence, experimental results from p75ExonIII-/- mice can significantly depend on the genetic background of the used mouse strains, especially when developmental or long-term effects of the p75ExonIII mutation are investigated. The background of the p75-deficient mouse strain used by Bengoechea et al. is not listed in their paper. But even with low or undetectable expression of s-p75 it cannot be excluded at present that s-p75 influences the developing nervous system, in this respect not unlike Abeta which Bengoechea et al. could not detect in developing and adolescent mice of the used AD model and which they considered to be responsible for the more severe sympathetic innervation defects in the p75-deficient AD mouse (compared to the p75-deficient mouse without overexpression of hAPP751).*

*If defects in the sympathetic nervous system of a p75 knockout mice expressing s-p75 or ts-p75 should be partly due to signaling of the respective p75 variant and if the reduction of sympathetic innervation observed in the p75ExonIII-/- J9 mouse is partly caused by Abeta (as indicated by the study of Bengoechea et al.) then it should be taken into consideration that aggregated Abeta might activate the two p75 variants. There is indeed evidence (presented in the full text of the Abeta-crosslinker-hypothesis) that, in addition to the known ("upper") binding site of p75 for Abeta within the four cysteine-rich domains, the stalk region of p75 contains a second specific binding site for Abeta that is adjacent to and perhaps overlapping the transmembrane domain ("stalk binding site"). Stimulation of a p75 mutant lacking the four cysteine-rich domains of full-length p75 with aged Abeta induces Ras activation similar to stimulation of wildtype p75, in contrast with a control construct that consists only of the extracellular and transmembrane domains of p75; peptide fragments from the putative stalk binding site for Abeta prevent Abeta-induced apoptosis in rat cerebellar neurons expressing full-length p75. These observations indicate that aged Abeta can bind and activate this p75 mutant, and they also suggest that Abeta can activate the s-p75 and ts-p75 proteins which include the entire stalk binding site for Abeta or part of it. Since s-p75 is expressed at substantially lower levels than full-length p75 (von Schack et al., 2001; Naumann et l., 2002), s-p75 signaling by itself might be too weak to trigger apoptosis or should require a longer period of Abeta stimulation for that than wildtype p75. This reflection might apply to the observation by Sotthibundhu et al. (2008) that overnight stimulation with oligomeric Abeta causes apoptosis in hippocampal neurons expressing full-length p75 but not in neurons from a p75ExonIII-/- mouse; interestingly, significant cell death was observed after stimulation of p75ExonIII-/- neurons with Abeta oligomers for 72 hours (Knowles et al., 2009) indicating perhaps an apoptotic influence of s-p75. During development, continual Abeta-induced signaling of s-p75 in the absence of full-length p75 might lead or contribute to deleterious effects.*

*How full-length p75 could protect neurons efficiently against Abeta and how the s-p75 variant could inhibit neurite outgrowth might be answered simultaneously. The Abeta-crosslinker-hypothesis postulates that short non-beta-sheet Abeta oligomers (that are pre-formed or produced ad hoc) can crosslink the p75 stalk binding site for Abeta with proteins such as APP, prion protein and alpha-synuclein and thereby mediate neurotrophic and neuroprotective cooperations between p75 and these proteins; these hypothetic cooperations are activated by neurotrophin or Abeta stimulation of p75 via the neurotrophin binding site and the upper Abeta binding site, implying that stimulation of p75 by Abeta can protect the cell against the toxicity of excess Abeta. Beta-sheet Abeta should compete with Abeta monomers and oligomers for binding to the stalk binding site and at sufficient concentrations inhibit the Abeta-mediated neurotrophic cooperations. In cells with wildtype p75, present s-p75 would competitively reduce the binding of aggregated Abeta to the Abeta stalk binding site of wildtype p75. This would allow p75 and newly formed or pre-existing short Abeta oligomers to establish more neurotrophic and neuroprotective cooperations of p75 and thereby increase neuroprotection by wildtype p75. The signaling of s-p75 activated by beta-sheet Abeta could amplify certain signaling pathways of p75 and support the signaling of Abeta-mediated*

*cooperations of p75, but as s-p75 probably lacks an upper binding site of Abeta (due to the lack of the neurotrophin binding site and the reported binding competition of NGF and Abeta for the upper binding site of Abeta on p75) it should not be neuroprotective by itself since links of s-p75 with p75 cooperation partners (mediated by bound oligomeric Abeta) could not be activated by neurotrophins or Abeta. At higher concentrations of aggregated Abeta, Abeta-mediated neurotrophic and neuroprotective cooperations of p75 would be reduced by increased binding of aggregated Abeta to the stalk binding site of full-length p75 for Abeta, and the signaling of activated s-p75 could amplify negative growth control by p75 and eventually accelerate Abeta-induced apoptosis via p75. Also, when s-p75 is activated by aggregated Abeta in the absence of wildtype p75 it may negatively influence neurite outgrowth and cell survival due to the lack of the neuroprotective effects of p75; in this case, stimulation of s-p75 by beta-sheet Abeta could induce cofactor-independent effects of p75 such as ceramide-induced Rho activation (inhibiting neurite outgrowth) or ceramide-dependent apoptosis. Altogether, the coexpressed s-p75 isoform might serve as a secondary receptor that is activated by aggregated Abeta and that enhances effects of p75-Abeta interaction.*

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Fombonne J, Rabizadeh S, Banwait S, Mehlen P, Bredesen DE (2009) Selective vulnerability in Alzheimer's disease: amyloid precursor protein and p75(NTR) interaction. Ann Neurol 65(3):294-303.
Abstract in Pubmed

*Comment: Fombonne et al. report a direct interaction of p75 and APP that crucially involves the first N-terminal 16 amino acids of Abeta within APP and that is negatively influenced by Abeta and nerve growth factor NGF. p75 expression diminishes the production of neurotrophic sAPPalpha and transcriptional effects of Fe65-APP interaction. Furthermore, in rat neuroblastoma B103 cells cotransfected with p75 and APP more cell death and higher caspase-3 activity can be observed than in cells expressing p75 or APP alone. The authors conclude that p75-APP interaction reduces the trophic effects of APP and leaves neurons with coexpression of p75 and APP vulnerable to Alzheimer's disease, in particular the cholinergic neurons of the basal forebrain.*

*The finding of the interaction between p75 and APP and the identification of the probable binding site on APP should be most valuable for the research into the role of p75 in both neuronal activity and neurodegenerative processes. Though the paper concentrates on possible detrimental effects of this interaction, the finding also opens the possibility of studying physiological functions of p75-APP interaction. Some interpretations by the authors, however, are not convincing.*

*1. The results from the used methods suggest that p75 and APP interact directly but they do not prove it. Since the C99 fragment of APP (in contrast with C83) interacts as well with p75 as full-length APP, the first 16 amino acid residues of Abeta in APP are essential for p75-APP interaction, and the interacting site on p75 should bind this Abeta segment. The known Abeta binding site within the neurotrophin-binding domain of p75 is not likely to mediate the p75-APP interaction since in the bioluminescence resonance energy transfer (BRET) study the relatively big YFP tag attached to the N-terminus of p75 should have sterically impeded such interaction. There is evidence (presented in the full text of the Abeta-crosslinker-hypothesis) that the stalk domain of p75 contains a second binding site for Abeta which in the BRET experiment could have been involved in the interaction. In the two-hybrid study both p75 binding sites for Abeta may have been able to bind the Abeta segment contained in the extracellular part of APP. In cells with endogenous Abeta, however, p75 and APP might be crosslinked by available or newly formed short Abeta oligomers via the high-affinity p75 stalk binding site for Abeta.*

*2. The observed reduction of p75-APP interaction by NGF and Abeta may depend on the (unlisted) period of NGF or Abeta incubation since both proteins activate p75 and lead to proteolysis of p75 and APP. Such proteolysis may mask the true extent of p75-APP interaction upon ligand-binding and may also underlie the reduction of p75-APP interaction observed in mice with Swedish and Indiana APP mutations; Abeta is increased in these mice and may stimulate p75. In addition, endogenous and added Abeta should compete with APP for binding to the p75 stalk binding site for Abeta and thus reduce p75-APP interaction.*

*3. The authors also show that p75 expression in B103 cells diminishes the production of sAPPalpha and increases the production of Abeta from C99 fragments of APP, and that the first effect is abolished by incubation of the cells (for 20 hours) with NGF or Abeta. p75 activation has been reported previously to regulate sAPPalpha shedding (Rossner et al., 1998), and the reduction of sAPPalpha production by unstimulated p75 could serve the regulation and amplification of neurotrophin and Abeta signaling effects by noise reduction and need not be an antitrophic effect.*

*4. Activated p75 increases Abeta production by elevating BACE1 activity through ceramide (cf. Costantini et al., 2005). A sufficiently high expression of p75 and APP with corresponding Abeta production may start a vicious cycle leading to cell death through stimulation of p75 by aggregated Abeta, especially when NGF and its specific receptor TrkA are absent; stimulated TrkA slightly lowers BACE1 activity (Costantini et al., 2005) and prevents ceramide generation by p75 in TrkA-p75 complexes (Plo et al., 2004). p75 activation by aggregated Abeta might be the cause of the observed increased cell death in B103 cells transfected with p75 and APP, and the generalized conclusion that coexpression of p75 and APP triggers cell death may depend on unphysiological experimental conditions. Such coexpression is not rare and obviously does not cause apoptosis under normal conditions.*

*The conclusion that the interaction between p75 and APP "shifts the effect of APP from a trophic one ... to an anti-trophic one" relies mostly on data from transfected B103 cells and represents a one-sidedly negative interpretation of this interaction. There are many hints in the literature supporting the view that such an interaction may have a positive, trophic role under physiological conditions and allow a direct functional cooperation of the two proteins, particularly in growth cones and synapses. The interaction may be mediated by Abeta oligomers via the p75 stalk binding site for Abeta that under pathological conditions could be hijacked by aggregate species of various amyloidogenic proteins binding to the p75 stalk either directly or through p75-bound Abeta. If this is correct then it is the interaction between p75 and Abeta that makes neurons vulnerable to Alzheimer's disease, and not the interaction between p75 and APP which is prevented by pathological interference with the interaction mechanism.*

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Abstract in Pubmed

*Comment: Knowles et al. show that Abeta oligomers bind to the neurotrophin receptor p75 (cf. Costantini et al., 2005), that p75 substantially contributes to Abeta-induced neuronal death and neurite dystrophy, and that a significant part of the toxicity of Abeta oligomers is independent of wildtype p75 (cf. e.g. Costantini et al., 2005). Using Förster resonance energy transfer (FRET) they observed an unusually strong FRET signal (50% reduction of donor emission) with donor FITC-Abeta and acceptor Cy3B-p75 that in their interpretation might be caused by the binding of multiple FITC-Abeta oligomers to p75; such binding could increase the probability of FRET occurrance or cause self-quenching of fluorescein and thus enlarge the apparent FRET signal. The FRET results and their interpretation would be consistent with the presence of a second binding site of Abeta on the p75 stalk close to the transmembrane domain which binding site is indicated by evidence presented in the Abeta-crosslinker-hypothesis. The binding of FITC-Abeta oligomers to both binding sites of Abeta on p75 could augment total energy transfer from FITC-Abeta to Cy3B-p75 or induce self-quenching of fluorescein and thereby diminish FITC emission and energy transfer to Cy3B-p75. With reverse fluorescence labeling (Cy3B-Abeta and FITC-p75), introduced FITC should be located within the upper half of extracellular human p75 (containing the N-terminus and all extracellular, FITC-binding lysines), and Cy3B-Abeta bound to the neurotrophin binding site might shield stalk-bound Cy3B-Abeta against energy transfer from p75-bound FITC, which should result in a weaker FRET signal (20% in the study).*

*To some extent the reduced but significant Abeta-induced cell death in cultured neurons lacking full-length p75 might be due to the expression of a truncated form of p75, s-p75, since apoptotic signaling has been demonstrated for a still shorter variant of p75 (Paul et al., 2004). According to the Abeta-crosslinker-hypothesis, aggregates of beta-sheet Abeta can bind to the juxtamembrane stalk and activate the truncated variants and might thus upregulate s-p75 and cause cell death.*

*The role of p75 in Abeta-induced neuronal degeneration described by Knowles et al. (and other researchers) contrasts with a neuroprotective effect of p75 against Abeta toxicity reported by Zhang et al. (2003), Costantini et al. (2005) and Bengoechea et al. (2009). The apparent conflict might be solved by the hypothesis that p75 can form neurotrophic and neuroprotective cooperations with APP, PrPc and other proteins via stalk-bound Abeta oligomers. High concentrations of administered Abeta oligomers or excessive endogenous Abeta, however, should soon produce beta-sheet Abeta, and the neuroprotective effect of p75 breaks down when beta-sheet Abeta (instead of Abeta mono- and oligomers) binds to the p75 stalk, prevents the neuroprotective cooperations of p75 and dimerizes and activates the receptor. In this view, Abeta-stimulated p75 would protect neurons against Abeta toxicity as long as the Abeta load is not too high and substantial neuroprotective cooperations of p75 occur whereas continual stimulation of p75 with high concentrations of Abeta species and the prevention of neuroprotective cooperations of p75 by beta-sheet Abeta would contribute to deleterious effects of Abeta.*

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Lauren J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM (2009) Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature 457:1128-1132.
Abstract in Pubmed

*Comment: Lauren et al. report that Abeta oligomers bind to PrPc and that the detrimental effect of Abeta on hippocampal LTP is not observed in PrPc knockout mice; PrPc presumably mediates this detrimental effect not by direct modulation of glutamate receptors but in an indirect way. The demonstration of a specific Abeta-binding site on PrPc opens up possibilities of exploring the role of PrPc in Alzheimer's disease and the role of Abeta in prion diseases; since a high-affinity PrPc binding site for Abeta should not be accidental it might also indicate a physiological role for Abeta. With picomolar concentrations of Abeta monomers and oligomers stimulating synaptic activity (Puzzo et al., 2008) certain species of Abeta oligomers should not be toxic under physiological conditions and their binding to PrPc may contribute to normal synaptic activity.*

*It has been proposed that some effects of PrPc involve an interaction of PrPc with a surface receptor and that the binding site of PrPc for this receptor overlaps segment 105-125 of PrPc (review Westergard et al., 2007). In their discussion, Lauren et al. suppose that "a putative PrPc-associated transmembrane co-receptor is likely to have a central role in Alzheimer's-disease-mediated neurodegeneration". As several publications indicate that the neurotrophin receptor p75 is essential for Alzheimer-like degeneration (e.g. Sotthibundhu et al., 2008) it is a candidate for such a co-receptor.*

*The demonstrated binding site of Abeta oligomers on PrPc (around 95-110) might support the Abeta-crosslinker-hypothesis which suggests an Abeta-binding site within PrPc segment 91-123 and permits a speculative explanation for the influence of PrPc on the detrimental effects of Abeta on hippocampal LTP observed by the authors: Aggregate species of Abeta can activate p75, and available or newly formed short Abeta oligomers may crosslink p75 and PrPc. The cooperation of stimulated p75 and PrPc would activate sphingomyelinase and NADPH oxidase in a synergistic feedforward process, and p75-Abeta-PrPc complexes could provide reactive oxygen species and elevated intracellular calcium required for components of p75 signaling. A "rapid inhibitory effect of p75(NTR) on NMDA-R currents that antagonizes TrkB-mediated NMDA-R potentiation" (Sandoval et al., 2007) should be increased by excess p75-activating Abeta and might be negatively influenced by a lack of PrPc. Excess Abeta might also induce oxidative stress and/or disturb cellular calcium homeostasis through disproportionate PrPc-receptor (and perhaps also PrPc-PrPc) crosslinking.*

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Muresan V, Varvel NH, Lamb BT, Muresan Z (2009) The cleavage products of amyloid-beta precursor protein are sorted to distinct carrier vesicles that are independently transported within neurites.
J Neurosci 29(11):3565-78.
Abstract in Pubmed

*Comment: Muresan et al. report that under normal conditions most of APP is cleaved early and the resulting fragments are sorted into distinct carrier vesicles that are transported independently and have different cellular destinations; this suggests that APP and its fragments have different functions. In particular, phosphorylated transmembrane C-terminal fragments of APP were preferentially observed in regions of lamellipodia and filopodia of growth cones that are involved in turning and advancement. As the crosslinking of p75 and APP postulated by the Abeta-crosslinker-hypothesis uses the Abeta region of*

*APP, p75 should be equally able to cooperate with full-length APP and certain transmembrane C-terminal fragments of APP (cf. Fombonne et al., 2009).*

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Renner M, Lacor PN, Velasco PT, Xu J, Contractor A, Klein WL, Triller A (2010) Deleterious effects of amyloid beta oligomers acting as an extracellular scaffold for mGluR5. Neuron 66(5):739-54.
Abstract in Pubmed

*Comment: The very interesting report by Renner et al. demonstrates Abeta-induced clustering of mGluR5 receptors and suggests that membrane-bound Abeta oligomers interact with mGluR5. Since chemical crosslinking of the receptor and application of Abeta oligomers produce similar synaptotoxic effects of mGluR5, the data point to (direct or indirect) Abeta-mediated crosslinking of mGluR5 receptors and thus support the idea that Abeta can function as a receptor crosslinker.*

*Both mGluR5 and the neurotrophin receptor p75 influence NMDAR-dependent long term depression elicited by low-frequency stimulation; while an mGluR5 antagonist largely prevents both induction and maintenance of LTD (e.g. Popkirov and Manahan-Vaughan, 2010), it is maintenance of LTD that is principally impaired in p75 knockout mice (Rösch et al., 2005). Modulation of mGluR5-induced LTD by p75 would agree with the crucial involvement of caspase-3 in LTD (Li et al., 2010), as stimulated p75 can induce caspase-3 activation, and with a likely interaction between p75 and NMDAR via PSD-95 and an inhibitory influence of p75 on NMDAR currents (Sandoval et al., 2007) which would also protect against excitotoxicity. p75 importantly contributes to Abeta-induced hippocampal degeneration (Sotthibundhu et al., 2008; Knowles et al., 2009), is activated by Abeta oligomers via an Abeta-binding site within its neurotrophin-binding region and has a second binding site for Abeta within its juxtamembrane stalk region that should serve Abeta-mediated crosslinking. Although a functional cooperation of mGluR5 and p75 without direct association of the two receptors is conceivable, the idea of an Abeta-mediated interaction of mGluR5 and p75 is appealing in view of the above arguments; such an interaction could also link mGluR5 with the NMDAR complex.*

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Reyes NA, Fisher JK, Austgen K, VandenBerg S, Huang EJ, Oakes SA (2010) Blocking the mitochondrial apoptotic pathway preserves motor neuron viability and function in a mouse model of amyotrophic lateral sclerosis. J Clin Invest 120(10):3673-9.
Abstract in Pubmed

*Comment: Reyes et al. report that the mitochondrial apoptotic pathway crucially contributes to degeneration and death of motoneurons in ALS of SOD1(G93A) mice. This pathway is also induced by the neurotrophin receptor p75 (see e.g. Troy et al., 2002), and earlier reports have linked p75 to ALS (e.g. Lowry et al., 2001). In particular, NGF from reactive astrocytes can cause motoneuronal apoptosis via p75 (Pehar et al., 2004).*

*However, neither p75 knockout (deletion of p75 ExonIII) in SOD1(G93A) mice (Küst et al., 2003) nor application of a cyclic decapeptide against the N-terminal region of p75 (Turner et al., 2004) do significantly influence onset and progression of ALS; on the other hand, application of antisense peptide nucleotides against p75 delays and attenuates ALS (Turner et al., 2003). These seemingly contradictory results can be reconciled by considering the (normally weak) expression of the truncated form of p75, s-p75, that can also be found in p75 ExonIII knockout mice and that (like p75) reaches significant levels in sciatic nerves of SOD1(G93A) mice by endstage ALS (Turner et al., 2009). s-p75 lacks the N-terminal cystein-rich domains of p75 and hence the neurotrophin- and Abeta-binding sites within this region but still encompasses a second Abeta-binding site in the extracellular juxtamembrane region of p75; evidence of this binding site is presented in the Abeta-crosslinker-hypothesis. The hypothesis suggests that oligomeric Abeta can crosslink p75 via this binding site with other surface proteins such as APP, alpha-synuclein and prion protein, and that this crosslinking represents an important physiological function of Abeta. Under pathophysiological conditions, however, beta-sheet aggregates of certain amyloidogenic proteins can cause p75-mediated cell degeneration and apoptosis when they form complexes with Abeta species and use Abeta to interact with the juxtamembrane binding site of p75 for Abeta. Amyloid aggregates that can activate p75 and s-p75 through this binding site include e.g. beta-sheet Abeta and NAC, a natural fragment of alpha-synuclein, and may also include secreted SOD1 aggregates since SOD1 and especially SOD1(G93A) can directly interact with Abeta (Yoon et al., 2009); TDP-43 too has been reported to interact with Abeta (Higashi et al., 2010) but it is unknown if TDP-43 is secreted as well. In addition, Abeta aggregates may contribute to peripheral motoneuron degeneration and to motoneuronal death by irregular activation of p75 and s-p75 as APP and Abeta are increased in certain muscle groups of ALS patients and of SOD1(G93A) mice (Koistinen et al., 2006). Although not the basic cause of ALS, p75 and s-p75 signaling may crucially aggravate the disease in the described ways.*

*Reyes et al. conclude that targeting processes that induce the mitochondrial apoptotic pathway might be a useful therapeutic strategy for ALS and related motoneuron diseases. The neurotrophin receptor p75 and its truncated form s-p75 certainly are worthwile objects of such research.*

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