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REVIEW

The functions and signaling pathways induced by the interactions of APP–related molecules with p75^{NTR}

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p75 neurotrophin receptor (p75^{NTR}) regulates diverse functions, including survival, differentiation, growth, and apoptosis of neurons, through its association with a number of molecules. Accumulating evidence shows that β-amyloid precursor protein (APP)–related molecules, which also regulate multiple neuronal functions, interact with p75^{NTR}. APP is cleaved by secretases to generate several proteins including soluble β-amyloid precursor protein alpha (sAPPα), sAPPβ, and amyloid β (Aβ). Binding of Aβ to p75^{NTR} induces neuronal death. In contrast, sAPPα directly interacts with p75^{NTR} to enhance neurite outgrowth through the activation of protein kinase A (PKA). This review focuses on the molecular mechanisms and functions occurring as a consequence of interactions of p75^{NTR} with APP–related molecules.

Keywords: APP; sAPP alpha; p75^{NTR}; neurite outgrowth; central nervous system

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Introduction

p75^{NTR} is a member of a large family of receptors, including tumor necrosis factor (TNF) receptors, Fas (Apo-1/CD95), RANK, CD40, and approximately 25 other members. p75^{NTR} mediates diverse functions, such as axonal elongation, neuronal survival, and modulation of synaptic transmission. p75^{NTR} regulates both positive and negative signals for certain neuronal functions [1, 2]. These bi-directional signals can be explained by the complex formation of p75^{NTR} with other receptors and multiple downstream intracellular signaling molecules. For example, p75^{NTR} is known to regulate axonal elongation both positively and negatively. Neurotrophin binding to p75^{NTR} decreases the activation of Rho small GTPase, resulting in the promotion of axonal elongation [3]. Indeed, p75^{NTR}-deficient mice show retarded outgrowth of intercostal nerves in the developmental stage [3]. In contrast, p75^{NTR} is also involved in axon growth inhibition through the activation of RhoA in the presence of myelin–derived inhibitors, such as myelin–associated glycoprotein (MAG), Nogo, and oligodendrocyte glycoprotein (OMgp) [4]. In this case, p75^{NTR} interacts with the Nogo receptor to form a receptor complex for these proteins [5]. Thus, the binding partners of p75^{NTR} may determine its downstream signaling and function.

p75^{NTR} associates with APP–related molecules [6-8]. Aβ peptide that accumulates in Alzheimer's disease (AD) induces cell death via p75^{NTR} in multiple types of cells, including some types of neurons [8-11]. A recent study demonstrated that the N-terminal fragment of APP (N-APP) interacts with p75^{NTR} [12]. Aβ and APP often show neurotoxicity, whereas sAPPα, which is a product of the non-amyloidogenic APP cleavage by α-secretase, has neuroprotective effects. Binding of sAPPα to p75^{NTR} stimulates neurite outgrowth [7]. In this review, we focus on the functions and signals induced by the interaction of p75^{NTR} with APP–related molecules in the central nervous systems (CNS).

Molecular profile of APP-related molecules

APP isoforms

APP is a single transmembrane protein with a long N-terminal domain in the extracellular space and a short C-terminal domain in the cytosol [13]. In mammals, the APP super family consists of APP itself, and APP-like proteins 1 and 2 (APLP1 and APLP2). APLP1 and APLP2 share sequence similarity with APP, although they lack Aβ domain [14,15]. APLP2 as well as APP are expressed ubiquitously, whereas APLP1 is exclusively expressed in the brain. The APP genes are located on chromosome 21 [16]. Alternative mRNA splicing of exon 7 and 8 generates the three major APP isoforms (APP695, APP751, and APP770) in the CNS [17-22]. APP751 and APP770, but not APP695, contain a Kunitz protease inhibitor (KPI) domain. In the brain, under the physiological condition, APP695 is predominantly expressed. In the AD brain, the expression levels of the other two APP isoforms seem to be increased [23-25]. These findings suggest that changes in the expression of each APP isoform may be associated with AD.

Proteolysis of APP

APP undergoes post-translational proteolysis to generate multiple fragments. These proteolytic products elicit pathological and physiological functions (Figure 1). There are two distinct pathways of APP metabolism: the non-amyloidogenic pathway, which avoids Aβ generation, and the amyloidogenic pathway, which generates Aβ. In the non-amyloidogenic pathway, APP is cleaved by α-secretase, releasing the large N-terminal ectodomain, sAPPα, from the cell surface. The remaining 83-amino-acid-long C-terminal fragment (C83) remains in the membrane. This fragment can be subsequently cleaved by γ-secretase, giving rise to small fragments, p3 and APP intracellular domain (AICD). In this pathway, the generation of Aβ is avoided, since α-secretase cleavage occurs within the Aβ sequence near the extracellular side

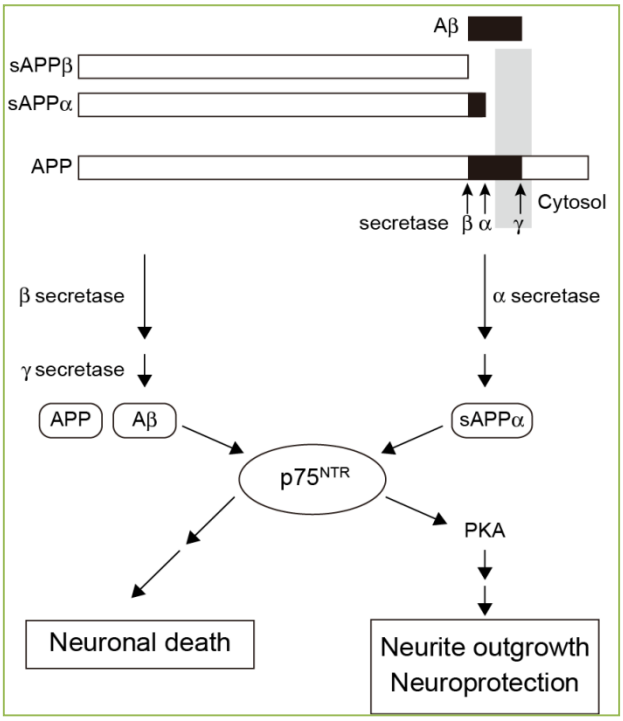

Figure 1. APP-related molecules and p75^{NTR}. α-secretase catalyzes the cleavage of APP to generate a soluble peptide, sAPPα. β-secretase cleaves APP to generate an alternate soluble peptide, sAPPβ, which is cleavedby γ-secretase to generate Aβ. The interaction of p75^{NTR} with Aβ or APP leads to neuronal death. In contrast, the interaction of p75^{NTR} with sAPPα promotes neuroprotection and neurite outgrowth through the activation of PKA.

of the plasma membrane [26, 27]. In the amyloidogenic pathway, APP is cleaved by β-secretase, which leads to the release of the N-terminal ectodomain, sAPPβ. The remaining 99-amino-acid C-terminal stub (C99) can be further cleaved by γ-secretase in a similar way as in the non-amyloidogenic pathway. This produces AICD and the amyloidogenic Aβ peptide [28].

Interactions of APP-related molecules with p75^{NTR}

In the adult brain, p75^{NTR} expression is restricted in the CNS, and the highest expression is observed in the neurons in the cholinergic basal forebrain, which represents a vulnerable region in AD [29-32]. p75^{NTR} mediates apoptosis induced by pro–nerve growth factor (pro-NGF), which is increased in the brains of AD subjects [33]. These observations suggest a possible association of p75^{NTR} and AD pathogenesis.

Although the expression levels of p75^{NTR} in the brains of patients with AD are contentious, most studies conclude that AD is associated with thedownregulation of tropomyosin-related kinase A (TrkA) expression with changed/unchanged expression of p75^{NTR} [34-36]. The expression levels of Aβ1–42 and p75^{NTR} in the

hippocampal cells from 12–15 month–old AD-triple transgenic mice (3xTg-AD mouse, which expresses APPs we, PS1M146V, and tauP301L mutations) are increased compared to that in hippocampal cells from age–matched wild-type mice [37]. These results are consistent with another observation that demonstrates elevated expression of $p75^{NTR}$ in hippocampal CA1 and CA2 neurons in human AD brains [34].

Accumulating evidence has revealed that $p75^{NTR}$ directly interacts with Aβ and APP, and that this interaction leads to apoptosis [6, 8]. It has been shown that aggregated Aβ induces apoptosis in NIH-3T3 cells stably expressing $p75^{NTR}$, but not wild-type control cells lacking the receptor. Normal neural crest–derived melanocytes, endogenously expressing $p75^{NTR}$, undergo apoptosis in the presence of Aβ [8]. Binding of Aβ to $p75^{NTR}$ induces the transcription of c-Jun mRNA. This leads to the activation of c-Jun N-terminal kinase (JNK) [38]. These results suggest that the interaction of $p75^{NTR}$ with Aβ induces apoptosis through the activation of JNK [8-10, 38].

Further, $p75^{NTR}$ is also involved in neuronal damage by interacting with APP. $p75^{NTR}$ directly interacts with APP, and the co-expression of $p75^{NTR}$ and APP induces cell death [6]. The interaction of $p75^{NTR}$ with APP is blocked in the presence of the ligands for $p75^{NTR}$, Aβ or NGF. Taken together, the interaction of $p75^{NTR}$ with Aβ and APP contributes to neuronal vulnerability in AD.

The effects of sAPPα on the neurons related with $p75^{NTR}$

Neuroprotective role of sAPPα

α-secretase catalyzes the cleavage of APP to generate sAPPα. This cleavage occurs within the Aβ sequence, avoiding Aβ generation. Unlike Aβ and APP, sAPPα has been shown to demonstrate neuroprotective effects both *in vivo* and *in vitro*. In the *in vivo* model of transient ischemia, administration of sAPPα protects CA1 hippocampal neurons against ischemic injury [39]. Treatment with sAPPα following a traumatic brain injury in rats improves functional outcome [40]. The growth factor-like domain (D1) and the E2 domain within the carbohydrate domain (D6a) of sAPPα (residues 28–123 and 316–498), which are able to bind to heparan sulfate proteoglycans (HSPGs), is found to be involved in the improvement of motor and cognitive outcomes against traumatic brain injury in rats, suggesting that HSPGs could mediate this response [41]. Furthermore, animal models that over express sAPPα have been developed. Knock-in of sAPPα rescues the abnormal phenotype of APP knockout mouse, such as reductions in the brain and body weight, grip strength deficits, and the impairment in spatial learning and LTP [42]. Transgenic mice with neuronal over-expression of APP, mutated at the α-secretase site, demonstrate the increased aggressiveness, disturbed responses to kainic acid and N-methyl-D-aspartate (NMDA), neophobia, and deficiency in exploratory behavior [43, 44]. These animal models confirm that sAPPα plays beneficial roles in the neurons.

sAPPα shows neuroprotective function against Aβ peptide-induced oxidative injury and glucose deprivation *in vitro* [45,46]. The C-terminus of sAPPα (residues 591–612) mediates *in vitro* neuroprotective effects against glutamate and Aβ toxicity, and heparinases greatly reduce this action [47]. sAPPα also protects PC12 cells and mature neurons from other toxic insults such as epoxomicin or UV irradiation by inhibiting the stress-triggered JNK-signaling pathway [48].

Neurite outgrowth and sAPPα

sAPPα has been shown to enhance neurite outgrowth [49,50]. Both the secreted forms of APP695 and APP770 promote neurite outgrowth in embryonic rat neocortical explants. This indicates that KPI domain is not responsible for neurite outgrowth-promoting activity of sAPPα.

The interaction of $p75^{NTR}$ with sAPPα contributes to sAPPα-induced neurite outgrowth [7]. Direct interaction of sAPPα with $p75^{NTR}$ was identified by co-immunoprecipitation and enzyme-linked immunosorbent assay (ELISA). EC50 of the interaction between sAPPα and $p75^{NTR}$ is 90 nM. In contrast, the affinity of NGF for $p75^{NTR}$ is higher (K_d 1–2 nM) [51, 52]. These observations indicate that the binding affinity of sAPPα for $p75^{NTR}$ is lower than that of neurotrophins. Furthermore, Binding of sAPPα to $p75^{NTR}$ promotes neurite outgrowth in the embryonic mouse cortical neurons. Protein kinase A (PKA) inhibitor KT5720 inhibits this function, suggesting that PKA activation is essential for sAPPα-induced neurite outgrowth.

Conclusions

As reviewed here, the interaction of $p75^{NTR}$ with Aβ and APP promotes neuronal cell death, while the interaction of $p75^{NTR}$ with sAPPα contributes to neurite outgrowth through the activation of PKA (Figure 1). These findings suggest that the balance of α-cleavage and β-cleavage of APP is critical to control cellular susceptibility to neurotoxic insults. It is notable that $p75^{NTR}$ mediates these opposite cues. The balancing mechanisms through $p75^{NTR}$ may regulate the CNS development and the determination of cellular fate after CNS injury.

Conflict of interests

The authors declare that they have no conflict of

interests.

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