Review

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Brothers in arms: proBDNF/BDNF and sAPPα/Aβ-signaling and their common interplay with ADAM10, TrkB, p75NTR, sortilin, and sorLA in the progression of Alzheimer's disease

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Abstract: Brain-derived neurotrophic factor (BDNF) is an important modulator for a variety of functions in the central nervous system (CNS). A wealth of evidence, such as reduced mRNA and protein level in the brain, cerebrospinal fluid (CSF), and blood samples of Alzheimer's disease (AD) patients implicates a crucial role of BDNF in the progression of this disease. Especially, processing and subcellular localization of BDNF and its receptors TrkB and p75 are critical determinants for survival and death in neuronal cells. Similarly, the amyloid precursor protein (APP), a key player in Alzheimer's disease, and its cleavage fragments sAPPα and Aβ are known for their respective roles in neuroprotection and neuronal death. Common features of APP- and BDNF-signaling indicate a causal relationship in their mode of action. However, the interconnections of APP- and BDNF-signaling are not well understood. Therefore, we here discuss dimerization properties, localization, processing by α- and γ-secretase, relevance of the common interaction partners TrkB, p75, sorLA, and sortilin as well as shared signaling pathways of BDNF and sAPPα.

Keywords: Alzheimer; amyloid precursor protein; APP; neurotrophic factors; neurotrophin; secretase.

Introduction: BDNF in Alzheimer's disease – data derived from human studies

The protein brain-derived neurotrophic factor (BDNF) plays an important role in the development and in the maintenance of the nervous system (Brigadski and Lessmann 2020; Huang and Reichardt 2001; Klein 1994; Park and Poo 2013). Its function as a regulator of neural plasticity and survival is well established (Edelmann et al. 2014; Huang and Reichardt 2001; Lu 2003). In addition, its contribution to different neurodegenerative and psychiatric diseases or disorders like diabetes mellitus is well accepted (Castren and Kojima 2017; Eyileten et al. 2017; Levy et al. 2018; Lima Giacobbo et al. 2019). Especially in the pathogenesis of Alzheimer's disease, the function of BDNF as a neuroprotective agent is well known. Several evidences, such as reduced level of BDNF in post-mortem AD brains or decreased level of BDNF in blood samples of patients, implicate a role of BDNF signaling in the pathophysiology of AD (Ng et al. 2019; Tapia-Arancibia et al. 2008). Furthermore, the inverse correlation between BDNF, its receptor TrkB, β-amyloidosis (Aβ plaques), and neurofibrillary tangles within specific regions of postmortem tissue strengthen the link between pathological features of AD and BDNF signaling (Ginsberg et al. 2019b). However, so far it is unknown whether or to which extent there is a causal relationship or only a coincident occurrence of imbalanced BDNF expression and AD. The disease itself is characterized by a slow progression of cognitive decline. In

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familial AD (FAD), preclinical symptoms are evident up to 25 years before onset of the disease (McDade et al. 2018). One of the earliest detectable markers is β-amyloidosis in the posterior cingulate cortex and precuneus of familial and sporadic AD (McDade et al. 2018; Palmqvist et al. 2017) which are important brain regions in regulating resting state functional connectivity of the default mode network (DMN) (Raichle 2015). β-amyloidosis is followed by hypoconnectivity within the DMN at very early preclinical stages of AD (McDade et al. 2018; Palmqvist et al. 2017). Dysregulation of the DMN have not only been linked to AD but also to major depressive disorder (MDD) (Mulders et al. 2015; Tozzi et al. 2020), which is one risk factor for later development of AD or even a hallmark of early AD pathology (Santiago and Potashkin 2021). Interestingly, involvement of BDNF is also suggested to play an important role in the pathophysiology of MDD (Castren and Kojima 2017; Levy et al. 2018), and changes in resting state functional connectivity from dorsomedial prefrontal cortex to posterior cingulate cortex were associated with changes in BDNF plasma level after infusions of healthy volunteers with ketamine, a drug to treat depressive symptoms (Woelfer et al. 2020). These findings indicate that BDNF might be involved in ketamine-induced changes of functional connectivity of the DMN. Further risk factors of AD such as type 2 diabetes, cardiovascular disease or inactivity have been also associated with imbalances in BDNF signaling (Eyileten et al. 2017; Hang et al. 2021; Zembron-Lacny et al. 2016), which strengthen a specific role of BDNF at very early stages of the disease. Furthermore, nonmedical therapies like physical activity have been associated with an upregulation of BDNF in human and animal model studies, respectively, and drug-based therapies with classical anti-dementives, such as donepezil, enhanced circulating levels of BDNF in patients (Alvarez et al. 2016; de Sousa Fernandes et al. 2020; Leyhe et al. 2008; Rehfeld et al. 2018; Walsh et al. 2020). Interestingly, donezepil treatment also shifted APP processing, a key event in progression of AD, from amyloidogenic to the nonamyloidogenic cleavage in differentiated human neuroblastoma cells (SH-SY5Y) (Zimmermann et al. 2004). Furthermore, Nigam et al. (2017) demonstrated that physical activity also led to increased nonamyloidogenic cleavage of APP in a transgenic AD animal model. In addition, BDNF decreased the amount of Aβ released from human neural cells in an α-secretase-dependent manner (Nigam et al. 2017) indicating a causal relationship between BDNF and APP signaling. This review addresses the important common players of both signaling pathways, which strengthen the assumed interplay of BDNF and APP signaling.

General aspects of BDNF processing, genetic variants and signaling

The secretory protein BDNF is expressed in neural and nonneural tissues and regulates multiple functions like neuroprotection, neurotoxicity, neurogenesis and neural plasticity (Brigadski and Lessmann 2020; Edelmann et al. 2014; Huang and Reichardt 2001). Multiple alternatively spliced mRNA variants of BDNF have been described (Adachi et al. 2014; Pruunsild et al. 2007; Timmusk et al. 1993), leading mainly to one protein isoform, the BDNF precursor protein (Pruunsild et al. 2007). This precursor protein is translated as proBDNF into the endoplasmic reticulum. Further posttranslational processing steps take place on its secretory path to the cell surface as well as extracellularly (Brigadski and Lessmann 2020). Proteolytic cleavage of proBDNF by proteases such as furin-like protein convertases PACE4, PC1 or PC5 (Mowla et al. 2001; Seidah et al. 1996), tissue type plasminogen activator (tPA)/plasmin proteolytic system, and matrix metalloproteinases (MMP) 3, 7 and 9 has been described (Gray and Ellis 2008; Lee et al. 2001; Pang et al. 2004). Proteolytical conversion of proBDNF (32 kDa) to the N-terminal cleavage fragment and mature BDNF (14 kDa) takes place intracellularly as well as extracellularly and depends on different determinants like the molecular equipment of the compartment, the surrounding pH value and calcium ion concentration (Lessmann and Brigadski 2009). Release of proBDNF and mature BDNF is mainly induced by electrical activity in neuronal cells (Brigadski and Lessmann 2020). However, constitutive secretion of BDNF, albeit to a lesser extent, has also been described (Lessmann and Brigadski 2009).

Concerning the release of BDNF in regard to Alzheimer's disease, one single nucleotide polymorphism of BDNF which is characterized by an amino acid substitution in the prodomain of BDNF was intensively discussed. However, so far, there are conflicting results whether this BDNF Val/Met polymorphism is associated with susceptibility or clinical features of AD (Bessi et al. 2020; Lim et al. 2020; Zhao et al. 2018). On the cellular level, the polymorphism has an impact on sorting and secretion of BDNF (Egan et al. 2003). Sorting sequences in the prodomain as well as in the mature domain of BDNF determine the main distribution of the protein to the regulated pathway of secretion (Brigadski et al. 2005; Chen et al. 2005). The single nucleotide polymorphism could be associated with an enhanced distribution of BDNF to the constitutive pathway of secretion, thereby reducing activity-dependent secretion of BDNF especially at the

synaptic site (Baj et al. 2013; Egan et al. 2003). However, neuronal and astrocytic release of either processed or unprocessed BDNF plays a major role not only during development of neural networks but also during inflammation, plasticity, and neuroprotective processes (Brigadski and Lessmann 2020).

Accordingly, unprocessed and processed BDNF exert different functions by preferentially binding to different receptor classes. Mature BDNF predominantly activates the TrkB receptor which belongs to the neurotrophin receptor family while proBDNF predominantly activates the p75 receptor, which is part of the tumor necrosis factor receptor superfamily (Almeida and Carlos 2014). BDNF-induced homodimerization of TrkB (Table 1) induces activation of rat sarcoma/mitogen-activated protein kinase (ras/MAPK), phospholipase C-γ/protein kinase C (PLC-γ/PKC) as well as phosphatidylinositol-3-kinase/Akt (PI3K/Akt) signaling pathway (Huang and Reichardt 2001). Heterodimerization of TrkB and p75 as well as heterodimerization of p75 and sortilin have also been described with preferential binding affinities for mature BDNF and proBDNF, respectively (Table 1). Intracellular signaling cascades which are mediated by p75 receptor leading to activation of c-Jun amino terminal kinase (JNK), Ras homolog gene family member A (RhoA), and nuclear factor kappa B (NF-κB). A wide spectrum of functions like neuronal survival, neurogenesis, neurite outgrowth but also apoptosis is promoted via p75 signaling (Colucci-D'Amato et al. 2020).

In summary, BDNF signaling via TrkB as well as p75 is important for neuroprotective and neurotoxic function in the CNS. Sorting of the protein to the specific secretory path as well as subcellular secretion site fine tunes the function of the protein via TrkB or p75 thereby inducing cell survival or cell death in CNS.

General aspects of APP processing and the relevance of its secreted fragments in AD

Processing of human amyloid precursor protein (APP) is a key event in the course of Alzheimer's disease, since toxic Aβ peptides as well as neurotrophic secreted amyloid precursor protein-α (sAPPα) are both generated under normal physiological conditions and an imbalance in the yield of those fragments is most likely causing the pathological condition of this disease (Eggert et al. 2018b; Haass et al. 1993). Toxic secreted Aβ species interact with different types of receptors in the central nervous system leading to synaptic failure and disrupted neuronal homeostasis (Sadigh-Eteghad et al. 2015).

APP is processed mainly in two different ways: the non-amyloidogenic and the amyloidogenic pathway (Figure 1). The amyloidogenic pathway starts with cleavage of APP via β-secretase. It is known that β-site APP-cleaving enzyme 1 (BACE1), a membrane bound aspartyl protease, is mostly responsible for the enzymatic activity of β-secretase (Vassar et al. 1999). β-Secretase cleavage results in the release of soluble sAPPβ and generation of the membrane bound ß-CTF. γ-Secretase is a membrane bound aspartic protease which can cut the ß-CTF liberating Aβ species of various lengths, which can be toxic (Trambauer et al. 2020), and the AICD (Weidemann et al. 2002).

In the non-amyloidogenic pathway, APP is firstly cleaved by α-secretase within the Aβ region, thereby precluding Aβ formation (Esch et al. 1990). In contrast to β-secretase, several proteases exist that function as α-secretases (Lichtenthaler 2011). These α-secretases are part of "a disintegrin and metalloprotease" (ADAM) family and ADAM10 is suggested to function as α-secretase with the highest physiological relevance for APP processing in neurons (Kuhn et al. 2010). Due to this cleavage, sAPPα is generated as well as the α-C-terminal fragment, which can be further converted by γ-secretase to release the non-pathogenic 3 kDa p3 peptide as well as the intracellular domain AICD. The secreted sAPPα fragment is known to have neurotrophic functions (Nhan et al. 2015). α-Cleavage of APP occurs mostly at the cell surface (Lammich et al. 1999) while processing of APP by β-secretase is carried out predominantly in endosomes (Vassar et al. 1999).

In the past years, additional APP-processing pathways have been identified which are responsible for the generation of further N-terminally cleaved APP fragments, including the δ-, η- and Meprin pathway reviewed in Eggert et al. (2018b) as well as cleavage by rhomboid protease RHBDL4 (Paschkowsky et al. 2016) or Calpain likely via indirect mechanism (Mahaman et al. 2019).

In the η-processing pathway, APP can firstly be cleaved at the η-cleavage site 504/505 by matrix metalloproteinase 5 (MT5), a zinc-dependent metalloprotease (Ahmad et al. 2006; Baranger et al. 2016; Willem et al. 2015). Subsequently, β- or α-secretase generate two peptides of 92 or 108 amino acids in length, designated as Aη-β or Aη-α peptides, respectively (Willem et al. 2015). In contrast to Aη-β, recombinant or synthetic Aη-α was reported to lower LTP as well as hippocampal neuronal activity *in vivo* and is therefore considered to be synaptotoxic (Willem et al. 2015).

The mammalian δ-secretase, also known for its synaptotoxic effects, facilitates the amyloidogenic pathway. δ-secretase (or Asparagine endopeptidase) is a lysosomal

Table 1: List of references for homo- and heterotypic interactions of the different receptors shown by different methods and in various cellular models.

Receptor homo- or heterodimer	Cell culture model	Method	References
TrkB homodimer	Cortex (monkey)	Chemical cross-linking	Ohira et al. (2001)
	HEK cells	Bimolecular fluorescence (BiFC) and Luciferase	Shen and Maruyama (2012)
	HEK cells	fragment complementation assay	Shen and Maruyama (2012)
	CHO cells	Chemical cross-linking	Shen and Maruyama (2012)
	HEK cells hippocampal	FRET	Ahmed and Hristova (2018)
	neurons	Blue native gels	Shen et al. (2019)
p75 NTR homodimer/trimer	COS7 cells	Disulfide linked dimers on SDS gels under non-	Vilar et al. (2009)
	COS7 cells	reducing conditions	Vilar et al. (2009)
	COS7 cells	Chemical cross-linking/immunoprecipitation	Vilar et al. (2009)
	Vibrio Cholerae	FRET	Vilar et al. (2009)
	HEK cells	ToxCAT assay of self-association of trans-	Sykes et al. (2012)
	HEK cells	membrane domains	Sykes et al. (2012)
	HEK cells	Chemical cross-linking	Anastasia et al. (2015)
	Cortical mouse neurons	FRET	Anastasia et al. (2015)
		Chemical cross-linking, disulfide linked trimers on SDS gels under non-reducing conditions	
		Disulfide linked trimers on SDS gels under non-reducing conditions	
Sortilin homodimer	Purified protein	Crystal structure	Januliene et al. (2017)
	Purified protein	Size exclusion chromatography	Januliene et al. (2017)
	Purified protein	EM	Januliene et al. (2017)
	Purified protein	Crystal structure	Leloup et al. (2017)
	Purified protein	SEC-SAXS	Leloup et al. (2017)
	HEK cells	Duo-link proximity ligation (PLA) assay	Leloup et al. (2017)
	HEK cells	FRET	Itoh et al. (2018)
	HEK cells	Co-immunoprecipitation	Itoh et al. (2018)
sorLA homodimer			Unknown so far
APP homodimer	SH-SY5Y cells	Chemical cross-linking, disulfide linked dimers	Scheuermann et al. (2001)
	SH-SY5Y cells	on SDS gels under non-reducing conditions	Scheuermann et al. (2001)
	COS7 cells	Co-immunoprecipitation,	Soba et al. (2005)
	COS7 cells	Chemical cross-linking	Soba et al. (2005)
	HEK cells	FRET	Kaden et al. (2009)
	HEK cells	FRET	Munter et al. (2007)
	FHK12 cells	ToxCAT assay of self-association of trans-	Munter et al. (2007)
	N2a cells	membrane domains	Eggert et al. (2009)
		Blue native gels	
TrkB-p75NTR heterodimer	A293 cells	Co-immunoprecipitation	Bibel et al. (1999)
	Hippocampal neurons	Co-immunoprecipitation	Zanin et al. (2019)
	Hippocampal neurons	FRET	Zanin et al. (2019)
TrkB-sortilin heterodimer	HEK cells, mouse cortical	Co-immunoprecipitation	Vaegter et al. (2011)
	and hippocampal neurons	SPR analysis	Vaegter et al. (2011)
	Renal cell carcinoma (RCC)	Co-immunoprecipitation	De la Cruz-Morcillo et al.
	cells		(2016)
TrkB-sorLA heterodimer	Mouse brain lysates	Co-immunoprecipitation	Rohe et al. (2013)
TrkB-APP heterodimer	HEK cell lysates	GST pulldown	Xia et al. (2020)
p75-sortilin heterodimer	HEK cells	Co-immunoprecipitation	Skeldal et al. (2012)
	HEK cells	FRET	Skeldal et al. (2012)
	Purified protein	Surface plasmon resonance (SPR) analysis	Skeldal et al. (2012)
	Renal cell carcinoma (RCC)	Co-immunoprecipitation	De la Cruz-Morcillo et al.
	cells		(2016)
p75-sorLA heterodimer			Unknown so far
p75-APP heterodimer	Mouse brain lysates, B103	Co-immunoprecipitation	Fombonne et al. (2009)
	cells	Proximity ligation assay (PLA)	Fombonne et al. (2009)
	Yeast two hybrid screen		Yi et al. (2021)
	neurons hippocampal		

Table 1: (continued)

Receptor homo- or heterodimer	Cell culture model	Method	References
Sortilin-sorLA heterodimer			Unknown so far
Sortilin-APP heterodimer	HEK cells, mouse brains	Co-immunoprecipitation	Yang et al. (2013)
	HEK cells	FRET	Yang et al. (2013)
	Purified protein	Surface plasmon resonance (SPR) analysis	Gustafsen et al. (2013)
	HeLa cells	Co-immunoprecipitation	Eggert et al. (2009)
sorLA-APP heterodimer	Purified protein	Surface plasmon resonance (SPR) analysis	Andersen et al. (2006)
	CHO-cells	Co-immunoprecipitation	Andersen et al. (2006)
	N2a cells	FLIM	Andersen et al. (2006)
	Purified protein	Surface plasmon resonance (SPR) analysis	Mehmedbasic et al. (2015)
	HEK cells	Co-immunoprecipitation	Mehmedbasic et al. (2015)
	HeLa cells	Co-immunoprecipitation	Eggert et al. (2009)

The following abbreviations are used: FRET, Foerster resonance energy transfer; EM, electron microscopy; FLIM, fluorescence lifetime imaging; SEC-SAXS, size exclusion chromatography-small angle X-ray scattering.

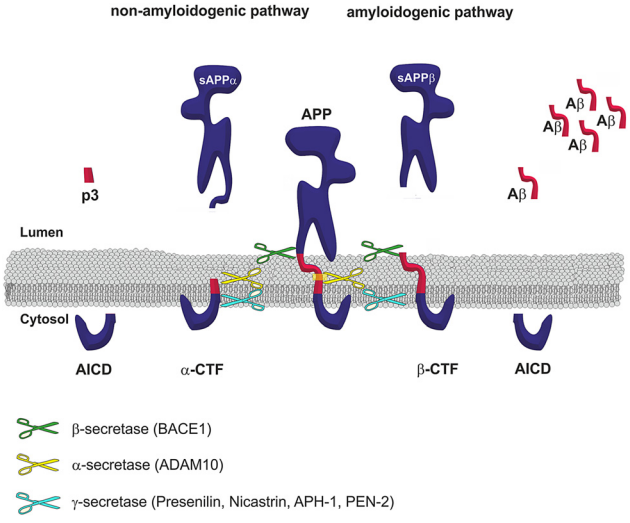

Figure 1: Classical canonical amyloidogenic and non-amyloidogenic pathway of APP processing.
The different secretases (α, β and γ) and their respective cleavage site are shown. The non-amyloidogenic pathway is initiated by α-secretase cleavage of APP. Thereby, soluble APPα (sAPPα) is released of the remaining C-terminal fragment, containing the APP Intracellular C-terminal domain (AICD) and the fragment p3. In the next step, the p3 fragment is cleaved off by γ-secretase. In the amyloidogenic pathway, APP is first cleaved by β-secretase and disintegrates into soluble APPβ (sAPPβ) and the membrane retained C-terminal fragment, containing the AICD and the Aβ region. This C-terminal fragment can be further cleaved by γ-secretase leading to the release of AICD and the Aβ peptide, which can form neurotoxic oligomers. The following abbreviations are used: β-site APP cleaving enzyme (BACE1), ADAM10 (a disintegrin and metalloproteinase), anterior-pharynx-defective protein-1 (APH-1), presenilin enhancer protein-2 (PEN-2).

cysteine protease that cleaves after asparagine residues (Chen et al. 1997, 1998). Activation of δ-secretase is autocatalytic and requires sequential removal of C- and N-terminal propeptides at different pH thresholds (Li et al. 2003). δ-secretase cleaves APP at residues N373 and N585 in the E2 domain of the APP ectodomain (Figure 2) and facilitates Aβ production by decreasing the steric hindrance for BACE1 (Zhang et al. 2015b). Position N585 is located only 11 aa N-terminal to the β-secretase cleavage site in APP at position D596. This is in line with results from a different study showing that inhibition of δ-secretase reduced β-secretase cleavage of APP and thereby improved cognitive functions in an AD mouse model (Zhang et al. 2017). Furthermore, the δ-secretase-cleaved APP (586–695) fragment was shown to induce amyloid plaques, synaptic impairments, and cognitive defects (Zhang et al. 2021).

In summary, APP processing is important for neuroprotective and neurotoxic function in the CNS. Processing of the protein by different secretases fine tunes the production of Aβ and sAPPα thereby inducing cell survival or cell death in CNS.

Cleavage fragments and common players in BDNF and APP-signaling

Processing and subcellular localization of BDNF and its signaling partners as well as APP and its cleavage fragments are critical determinants for survival and death of neuronal cells. Both signaling pathways are linked via crosstalk and feedback mechanism. Important common players of sorting and processing of BDNF receptors and APP like α-secretase, γ-secretase, sortilin and sorLA indicate a relationship of both signaling pathways and may regulate the balance between neuroprotective and neurotoxic effects in the progression of Alzheimer's disease. In the following, we discuss the relationship between

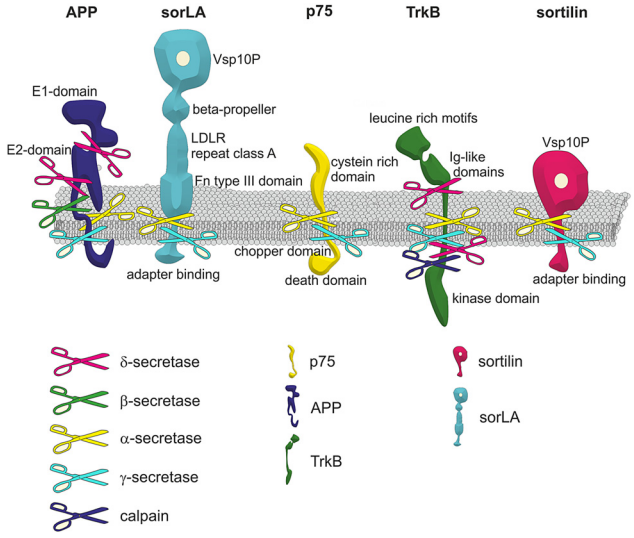

Figure 2: Domain structures and cleavage sites of APP- and BDNF-signaling partners.
Schematic representation of APP, sorLA, sortilin, p75 and TrkB receptor illustrates extracellular and intracellular domains of the different transmembrane proteins as well as the respective cleavage sites of the different proteases. The extracellular domain of APP consists of E1 linked by an acidic domain to E2. δ-secretase cleaves APP at residues N373 and N585 at the respective boundaries of the E2 domain. α- and β-secretase cleave the ectodomain of APP in the juxtamembrane region leading to the cleavage products sAPPα or sAPPβ, respectively. γ-secretase cleavage of APP is responsible for the generation of AICD. The co-receptors sorLA and sortilin share similar domain structures. Both consist of an extracellular Vps10 domain and an intracellular adaptor binding site. In addition, sorLA contains of multiple LDLR repeats and Fn type III domain. Both, sorLA and sortilin have been shown to be proteolytically processed by α- and γ-secretase in juxtamembrane regions. TrkB recognizes BDNF with its leucine-rich domain and one of the Ig-like domains. The intracellular catalytic tyrosine kinase domain mediates intracellular signaling transduction. TrkB can be cleaved by δ-secretase in the boundary of Ig-like domain 2 leaving the ligand binding domain of TrkB. Furthermore, TrkB can be cleaved by α-secretase in the juxtamembrane region which results in the generation of a longer ECD of TrkB as cleaved by δ-secretase. On the intracellular site, cleavage of TrkB by γ-secretase and δ-secretase upstream of the shc-binding site has been described as well as cleavage of TrkB by calpain in between the shc-binding site and the kinase domain of TrkB. P75 includes cysteine-rich domains in the extracellular region as well as one chopper domain and one death domain in the intracellular part of the protein. Cleavage of p75 by α- and γ-secretase has been reported. In contrast to TrkB, p75 contains no catalytic domain. Activation of p75 is postulated by uncovering of intracellular signaling site after ligand-binding-induced conformational change of the receptor. The following abbreviations are used: Vps10P (Vacuolar protein sorting 10), AICD (APP intracellular domain), LDLR (Low Density Lipoprotein Receptor), Fn type III (fibronectin type III), Ig (immunoglobulin-like), APP (Amyloid precursor protein), TrkB (Tropomyosin receptor kinase B), sorLA (sortilin-related receptor) L (DLR class) A.

cleavage fragments and common players in BDNF and APP-signaling by addressing dimerization properties, localization and processing.

sAPPα: general aspects

sAPPα is a neuroprotective and neurotrophic protein, derived from the parent APP molecule. It has synaptogenic, LTP facilitating and memory enhancing properties (Richter et al. 2018; Weyer et al. 2014). A different aspect of the physiological function of sAPPα is its ability to stimulate proliferation of neural stem cells (NSCs) (Hayashi et al. 1994; Ohsawa et al. 1999), embryonic stem cells (Porayette et al. 2009), and adult progenitor cells (Caille et al. 2004; Demars et al. 2011). sAPPα also plays an essential role in survival of neurons shown in different cell culture studies (Furukawa et al. 1996; Goodman and Mattson 1994; Smith-Swintosky et al. 1994; Turner et al. 2007). The identity of the sAPPα receptor is not fully resolved yet, but different studies implied a role of GABAB (Rice et al. 2019), Na/K-ATPase (Dorard et al. 2018), nicotinic α7 acetylcholine receptors (α7-nAChRs) (Richter et al. 2018), and NMDA receptors (Gakhar-Koppole et al. 2008; Mockett et al. 2019).

A wealth of data suggested NMDA receptors as a receptor for sAPPα (Ishida et al. 1997; Moreno et al. 2015; Taylor et al. 2008). These results are in line with reports showing that full length APP can interact with GluN1/GluN2 receptors and enhance their cell surface expression (Cousins et al. 2009, 2015; Innocent et al. 2012). A recent study demonstrated that sAPPα-induced synaptic plasticity in hippocampal neurons is mediated via cooperation of NMDA and α7-nAChRs receptors, resulting in enhanced transcription and translation of Arc via CaMKII, MAPK, and PKG signaling (Livingstone et al. 2019). Similar to BDNF, nanomolar amounts of sAPPα promote a gradual increase in Arc mRNA, but with a stronger effect for BDNF (El-Sayed et al. 2011).

This is in accordance with an earlier investigation which identified α7-nAChRs as a crucial physiological receptor for sAPPα for its LTP facilitating function (Richter et al. 2018). This signaling pathway is paralleled by BDNF that can modulate neuronal output in part by controlling α7-nAChR levels (Massey et al. 2006; Zhou et al. 2004). The contribution of BDNF to synaptic plasticity in the hippocampus but also in many other brain areas is well known (Edelmann et al. 2014, 2015; Leal et al. 2017; Lu et al. 2014; Meis et al. 2020) and the modulation of NMDAR function by BDNF is also well accepted (Bartlett and Wangy 2013). Similar, LTP-inducing stimuli release BDNF and also

release/generate sAPPα (see below) which makes it likely that both factors cooperate during hippocampal LTP. Interestingly, also donezepil treatment of cells suggested again that sAPPa and BDNF are players in the same neurotrophic pathway. Increased neurite elongation and improved cell viability have been shown through activations of PI3K, BDNF, β-catenin and α7-nAChR receptors by a combinatorial mixture of donezepil, cilostazol plus aripiprazole, which also activated ADAM10 leading presumably to increased sAPPα levels (Heo et al. 2020).

Production of sAPPα and similarities to BDNF release

Several stimuli like high frequency stimulation (HFS) of hippocampal neurons (Nitsch et al. 1993), NMDA receptor activation (Hoey et al. 2009), AMPA receptor activation (Hoey et al. 2013), protein kinase C activation (Caputi et al. 1997), stimulation of muscarinic M1 receptors (Caccamo et al. 2006; Farber et al. 1995; Nitsch et al. 1992), M3 acetylcholine receptors (Nitsch et al. 1992), mGluR1 glutamate receptors (Nitsch et al. 1997) or forskolin (Robert et al. 2005) have been reported to promote α-secretase-mediated cleavage of APP (Figure 3). Interestingly, similar stimuli have been described to induce release of BDNF (Figure 3) thereby activating TrkB receptor (Brigadski and Lessmann 2020). For example, BDNF secretion was shown to depend on mGluR1 activation in different cell types (Bagayogo and Dreyfus 2009; Balkowiec and Katz 2002; Canossa et al. 2002; Jean et al. 2008). Furthermore, HFS is a well-known stimulus to induce activity-dependent secretion of BDNF in hippocampal neurons as well as in other brain areas (Balkowiec and Katz 2002; Hartmann et al. 2001; Kojima et al. 2001; reviewed in Brigadski and Lessmann 2020). Just as for sA PPα, release of BDNF was described to be frequency-dependent and could be blocked by TTX (Balkowiec and Katz 2002; Hartmann et al. 2001). Electrically induced BDNF release upregulates the TrkB receptor-mediated PLC/PKC-signaling cascade during hippocampal LTP (Gartner et al. 2006; Gruart et al. 2007; Minichiello et al. 2002). Furthermore, calcium influx via NMDA receptors contributes to BDNF release (Hartmann et al. 2001; Matsuda et al. 2009; Park 2018) as well as to non-amyloidogenic APP processing (Hoey et al. 2009).

While the time course of BDNF release as well as the cellular source of BDNF is intensively analyzed, similar investigations are missing for the release/cleavage of sAPPα. Merely quantifying the amount of sAPPα by Western blots does not clarify the original cellular source of sAPPα or whether the increase in extracellular cleavage

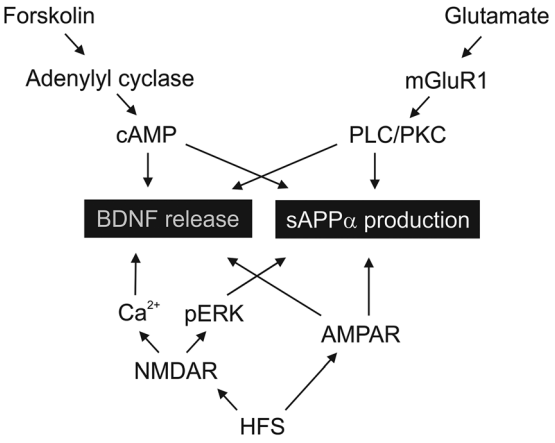

Figure 3: Production of sAPPα and similarities to BDNF release. Several stimuli like high frequency stimulation (HFS), activation of NMDAR, AMPAR and mGluR1 have been reported to promote α-secretase-mediated cleavage of APP as well as release of BDNF. However, release of BDNF and production of sAPPα, respectively, might occur on a different time scale.

product is derived from exocytosis of sAPPα-containing vesicles or from processing of APP at surface membrane (Nitsch et al. 1993). Though, it was reported that a small number of synaptic vesicles contains APP, which can be released during neuronal activity (Groemer et al. 2011). While BDNF is immediately secreted into extracellular space after electrical stimulation (Brigadski et al. 2005; Hartmann et al. 2001; Kojima et al. 2001), the onset of APP cleavage seems to be delayed (Nitsch et al. 1993, 1997). Therefore, release of BDNF and release of sAPPα, respectively, might occur on a different time scale. However, it needs to be clarified whether BDNF supports only non-amyloidogenic processing of APP (Nigam et al. 2017) or whether BDNF and sAPPα might be also co-released under certain conditions to support neuroprotective functions such as survival, synaptogenesis or neurite outgrowth.

Role of sAPPα during neurite outgrowth: resemblance to BDNF signaling

Early studies in AD research already demonstrated that, similar to BDNF, sAPPα can promote neurite (Araki et al. 1991; Clarris et al. 1994; Small et al. 1994) as well as axonal outgrowth (Chasseigneaux et al. 2011; Young-Pearse et al. 2010). Several APP domains in the extracellular part of the protein seem to be involved in these functions, including the N-terminal APP96–110 region located in the first heparin-binding domain and the APP319–335 region, which contains the RERMS motif within the E2 domain (Jin et al. 1994; Ninomiya et al. 1993, 1994). In addition,

various studies investigated the signaling pathways involved in neurite extension due to sAPPα. Chasseigneux et al., for example, demonstrated that both, sAPPα and sAPPβ, were able to specifically enhance axonal growth at nanomolar concentrations via early growth response protein 1 (Egr1) signaling in cultures of embryonic cortical neurons (Figure 4) (Chasseigneaux et al. 2011). BDNF/TrkB signaling was also shown to increase Egr1 expression in primary neurons through activation of MAPK signaling (Figure 4) (Alder et al. 2003; Calella et al. 2007). However, dendritic and not axonal differentiation was mediated via BDNF/Egr1-dependent mechanism (Calella et al. 2007). Another report indicated that sAPPα as well as depolarization induced neurite elongation and that both, sAPPα and depolarization, induced MAPK/ERK signaling via activation of NMDA receptors (Figure 4) (Gakhar-Koppole et al. 2008). Depolarization-induced ERK phosphorylation was evident on a very fast time scale after activation of NMDAR while acute addition of sAPPα alone did not lead to ERK activation. However, inhibition of APP processing by α-secretases prevented depolarization-induced neurite outgrowth and continuous generation of sAPPα was necessary for depolarization-induced ERK phosphorylation, indicating that sAPPα promotes MAPK/ERK translocation by an unknown mechanism (Gakhar-Koppole et al. 2008). Interestingly, Patterson et al. (2001) described different forms of electrically induced BDNF-dependent LTP that required phosphorylation and subsequent nuclear translocation of phosphorylated MAPK (Figure 4). While adenylyl cyclase activator forskolin increased MAPK phosphorylation by an unknown mechanism, translocation of the activated MAPK was dependent on BDNF/TrkB signaling (Patterson et al. 2001). BDNF/TrkB signaling might therefore support translocation of phosphorylated MAPK which in turn is activated via depolarization-dependent nonamyloidogenic APP cleavage.

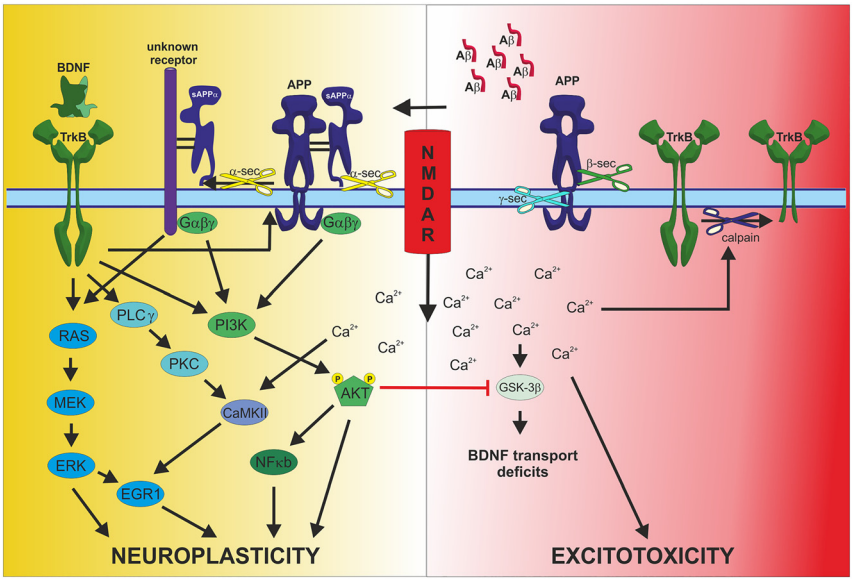

Figure 4: Interconnected signaling pathways of BDNF, sAPPα and Aβ in balancing neuroplasticity or excitotoxicity.
sAPPα and BDNF can modulate several pathways involved in neuroplasticity processes like neurite outgrowth, synaptic integrity, and neuroprotection including the PI3K/Akt, NF-κB, and MAPK/Erk/Egr1 signaling. sAPPα activation of the PI3K/Akt survival pathway depends on the presence of full length APP and its intracellular G-protein interaction motif or might be induced via sAPPα binding to an unknown receptor. sAPPα also reduces tau-pathology by inhibiting GSK3β activity via the PI3/Akt pathway. In the case of BDNF, neuronal survival is also mediated along the PI3K/Akt pathway. In addition, BDNF-induced activation of NF-κB promotes survival as well as neurite outgrowth. Convergence of BDNF and sAPPα signaling might protect from age-related changes in NF-κB function. Binding of BDNF dimer to the TrkB receptor also activates the RAS/MAPK signaling pathway as well as nuclear translocation of phosphorylated ERK thereby promoting survival, spine integrity and LTP. Phosphorylation of the TrkB receptor activates the PLC-γ pathway, generating inositol-1, 4, 5-triphosphate (IP3) and diacylglycerol (DAG). The PLC-γ/IP3 pathway results in calcium release from intracellular stores, which in turn activates Ca^{2+}/CaMKII. CaMKII can in turn induce the expression of Egr1. TrkB receptor also promotes α-secretase cleavage of APP by activating ADAM10. In contrast, Aβ oligomers induce NMDA receptor-dependent inward calcium ion (Ca^{2+}) currents, membrane depolarization, oxidative stress and apoptotic cell death. Aβ coupled excitotoxicity also stimulates TrkB cleavage by calpain in a calcium dependent manner. Furthermore, Aβ-induced deficits in BDNF transport were described to be mediated by activation of GSK-3β. The following abbreviations are used: PI3K (phosphoinositide 3 kinase), Akt/protein kinase b (AK strain transforming), GSK-3β (glycogen synthase kinase 3β), RAS (rat sarcoma), MEK (mitogen-activated protein kinase kinase), ERK (extracellular signal related kinase), EGR1 (Early growth response 1), PLC-γ (phospholipase C-γ), PK1, CaMKII (Calcium/Calmodulin dependent protein kinase II), Gαβγ (trimeric G protein), NMDAR (*N*-methyl-D-aspartate receptor), TrkB (Tropomyosin receptor kinase B).

Neuroprotective function of sAPPα and interconnections to BDNF

There is also evidence for sAPPα-mediated neuroprotective mechanisms. Several studies suggested that the neuroprotective function of sAPPα results from activation of phosphatidylinositol-3-kinase (PI3K)/Protein Kinase B (PI3K/Akt) (Cheng et al. 2002; Jimenez et al. 2011) similar to BDNF/TrkB signaling (Figure 4) (Rai et al. 2019). In the case of sAPPα, this pathway can either be mediated via binding of sAPPα to full length APP followed by activation of a trimeric G protein via the APP C-terminus (Milosch et al. 2014) or might be activated by binding of sAPPα to an unknown receptor. Synthetic sAPPα, acting through IGF-1R and insulin receptors stimulated Akt-GSK-3β phosphorylation in N2a cultures, thereby indicating a neuroprotective mechanism in aging AD mice (Jimenez et al. 2011). Interestingly, BDNF and IGF-1, are upregulated in response to physical exercise that might counteract memory impairment upon aging (Kim et al. 2019; Park et al. 2011). It was further reported that survival-promoting properties of sAPPα are possibly mediated by the ability of sAPPα to activate NF-κB and to stabilize Ca^{2+} homeostasis (Figure 4) (Guo et al. 1998). In line with this, a different study showed that sAPPα activates NF-κB transcription in hippocampal neurons, which was neuroprotective (Barger and Mattson 1996). Exposure of neurons to sAPPα resulted in a decrease in the level of IκB and an increase in NF-κB DNA binding activity, both of which were blocked by wortmannin, suggesting that the transcription factor NF-κB may be a downstream target of the PI3K–Akt pathway (Figure 4) (Cheng et al. 2002). BDNF has also been reported to regulate NF-κB expression via TrkB activation as well as p75 receptor (Gavalda et al. 2009; Kairisalo et al. 2009; Lipsky et al. 2001; Reichardt 2006). However, cellular functions mediated via BDNF/NF-κB signaling are dependent on cell type as well as on developmental stage (Gavalda et al. 2009; Lipsky et al. 2001). While BDNF and NDMAR-dependent increase in NF-κB-induced gene transcription promoted survival of granule cell cultures (Lipsky et al. 2001), specifically neurite outgrowth was mediated by BDNF/NF-κB signaling in cultures of nodose ganglion neurons at E17 but not at P0 (Gavalda et al. 2009). Further studies need to clarify, whether convergence of BDNF and sAPPα signaling might protect from age-related changes in NF-κB function.

Neuroprotective functions of BDNF and sAPPα have also been demonstrated to be regulated by physical exercise. Acute exercise leads to two to three-fold increased BDNF levels compared to resting conditions and correlates positively with amelioration in cognitive functions in humans (Griffin et al. 2011; Rasmussen et al. 2009) and also in mice (Adlard et al. 2005a; Sleiman et al. 2016). A recent study indicated that after a three-week running wheel exercise of ~7–9 month old APP/Presenilin 1 (APP/PS1) double mutant transgenic mice showed significantly increased levels of sAPPα and BDNF with concomitant reductions of Aβ40 and Aβ42 levels in the hippocampus of this AD mouse model (Nigam et al. 2017). This is in line with results from different reports which demonstrated that increased physical activity decreases Aβ levels in different mouse or rat models of AD (Adlard et al. 2005b; Azimi et al. 2018; Liu et al. 2013; Maesako et al. 2012; Vasconcelos-Filho et al. 2020; Zhao et al. 2015) as well as BACE 1 protein expression (Alkadhi and Dao 2019). Interestingly, different training durations did not lead to ameliorations on a transcriptional level in three-month-old 5xFAD (Wierczeiko et al. 2021). Nigam et al. (2017), additionally demonstrated that BDNF- treatment enhanced α-secretase processing of APP (Figure 4) with a concomitant reduction of Aβ peptides in cultured human neuroblastoma cells. BDNF did not induce increased ADAM10 expression, but its redistribution from the cell surface to intracellular locations. This finding is in line with reports, which suggest that regulated α-secretase activity occurs intracellularly (Skovronsky et al. 2000). Conclusively, BDNF-mediated upregulation of α-secretase processing of APP might be one mechanism how exercise protects the brain against AD (Nigam et al. 2017).

Aβ toxicity

Aβ toxicity plays a major role in Alzheimer's disease. There are several Aβ species generated of which Aβ40 is the major isoform (Steiner et al. 2018). However, less abundant species such as Aβ42 and its N-terminally truncated isoforms show a stronger aggregation behavior and higher neurotoxicity (Portelius et al. 2011). Among the Aβ species studied so far, Aβ25-35 represents the shortest fragment of Aβ peptides processed *in vivo* and is one of the most toxic species by inducing neuronal loss (Kaneko et al. 2001; Millucci et al. 2010).

Mutual influence of Aβ and BDNF expression

Concerning BDNF-signaling, the neurotrophic factor has been shown to prevent neuronal toxicity induced by Aβ1–42 and Aβ25–35 (Tapia-Arancibia et al. 2008; Wang

et al. 2020). Treatment of cells with a Trk inhibitor K252A before exogenous application of BDNF, completely blocked the protective effects of BDNF against Aβ toxicity, showing that these effects involve TrkB receptor activation (Arancibia et al. 2008). Consistent with these findings, it could be demonstrated that BDNF reduced Aβ levels *in vitro* (Rohe et al. 2009). Furthermore, BDNF deprivation enhanced Aβ content in extracellular medium of hippocampal and cortical cultures (Matrone et al. 2008; Wang et al. 2019), and levels of BDNF mRNA negatively correlated with the ratio of Aβ42/Aβ40 in three transgenic AD mouse strains (Peng et al. 2009). In turn, Aβ application resulted in a biphasic response on BDNF mRNA level showing an early increase (Aliaga et al. 2010) and a later decrease of BDNF mRNA (Aliaga et al. 2010; Garzon and Fahnestock 2007; Tong et al. 2001). Furthermore, mature BDNF was reduced after intracerebroventricular injection of Aβ1–42 in rodent hippocampus (Zhang et al. 2015a), and an increase in proBDNF/mature BDNF ratio was associated with reduced activity of tPa after treatment with Aβ25–35 (Angelucci et al. 2019; Gerenu et al. 2017) indicating that proteolytic cleavage of BDNF was also affected by Aβ25–35 (Gerenu et al. 2017). In addition, fibrillary Aβ25–35 selectively increases the mRNA level of BDNF receptor isoform TrkB-T1 which is described as a dominant negative regulator of full length TrkB. Additionally, Aβ25–35 promotes truncation of full length TrkB by calpain (see also chapter "TrkB isoform expression in AD" and "proteolytic truncation of TrkB in AD") (Jeronimo-Santos et al. 2015). All these data indicate that Aβ and BDNF influence expression and processing of each other.

Influence of Aβ on BDNF trafficking

Besides the impact of Aβ species on BDNF expression and cleavage, transport of BDNF-containing vesicles was also affected by Aβ. Already acute application of Aβ1–42 oligomers reduced the speed of BDNF-containing vesicles in hippocampal neurons (Seifert et al. 2016). Long term treatment with Aβ or overexpression of hAPP dramatically changed the dynamics of anterograde and retrograde BDNF transport (Poon et al. 2013; Seifert et al. 2016). Aβ-induced deficits in BDNF transport were described to be independent of tau protein and were mediated by calcineurin-dependent activation of GSK3β (Figure 4) (Gan and Silverman 2015; Ramser et al. 2013). Interestingly, transport deficits of BDNF-containing vesicles have been also observed in young 5xFAD hippocampal cultures (Seifert et al. 2016). This transgenic mouse line is characterized by a rapid accumulation of Aβ1–42, starting at the age of 1.5 months (Oakley et al. 2006). Deficits in BDNF transport kinetics could be already observed at DIV 12 in these cultures (Seifert 2016). In the same AD mouse model, numbers of Ca^{2+}-oscillations as well as numbers of cells exhibiting Ca^{2+}-activity were significantly reduced at DIV 21 (Mitroshina et al. 2020). Changes in Ca^{2+}-oscillations could be reproduced by chronic Aβ1-42 application and neuronal network activity was disturbed as revealed by multi-electrode array measurements in cultures of hippocampal wildtype neurons (Mitroshina et al. 2020). These effects of Aβ1-42 on neuronal networks could be prevented to a large extent by additional BDNF application (Mitroshina et al. 2020), indicating that transport deficits of BDNF-containing vesicles are very early events of amyloid pathology (Figure 4).

In neuronal cells, the influence of Aβ on transport of BDNF-containing vesicles seems to be specific, since Aβ itself neither had an influence on high potassium-induced release of BDNF (Seifert et al. 2016) nor on internalization of BDNF receptors (Poon et al. 2013). In addition to the impact of Aβ on BDNF transport, the precursor APP might also influence BDNF transport by acting as a motor-cargo linker for BDNF-containing vesicles (Brunholz et al. 2012). Further studies need to clarify the putative function of APP in transport of BDNF-containing vesicles.

Conclusive remarks on the interplay of Aβ and BDNF

There are further links between BDNF signaling and the amyloidogenic and non-amyloidogenic pathway of APP (Arancibia et al. 2008; Nigam et al. 2017; Zheng et al. 2010). Conclusively, Aβ-induced reductions in LTP could be rescued by BDNF (Criscuolo et al. 2015; Sharma et al. 2017). However, this rescue was, at least partially, dependent on inhibition of Ca^{2+}-influx through NMDAR, thereby reducing cleavage of full length TrkB by calpain (Figure 4) (see also chapter: proteolytic truncation of TrkB in AD) (Jeronimo-Santos et al. 2015; Tanqueiro et al. 2018). In addition, cognitive impairment could be recovered by BDNF via Erk activation after intracerebroventricular injection of Aβ1–42 (Figure 4) (Zhang et al. 2015a). In this line, cognitive impairment was also rescued by BDNF-signaling in transgenic AD mice (Braschi et al. 2021; Tanila 2017; Ye et al. 2012), and AD transgenic mice with chronically reduced BDNF level showed an earlier onset of cognitive decline (Psotta et al. 2015) indicating interconnections of BDNF signaling and APP processing in balancing plasticity processes and neuronal excitotoxicity (Figure 4).

TrkB receptor: general aspects to TrkB expression in AD

The TrkB receptor belongs to the neurotrophin receptor family. Three of the alternatively spliced mRNA isoforms, namely full length TrkB, TrkB-T1 and TrkB-T-Shc, have been implicated in the pathology of AD (Allen et al. 1999; Ferrer et al. 1999; Ginsberg et al. 2019b; Salehi et al. 1996; Wong et al. 2012a, 2012b). The most prominent isoform, the full length TrkB, consists of leucine-rich motifs, cysteine-rich domains and immunoglobulin-like domains in the extracellular region and an intracellular catalytic kinase domain (Figure 2) (Barbacid 1994; Strohmaier et al. 1996). Gene expression of full length TrkB inversely correlated with antemortem cognitive assessment measures as well as diffuse Aβ plaques in the entorhinal cortex (Ginsberg et al. 2006, 2019a). The two other isoforms associated with AD, TrkB-T1 and the TrkB-T-Shc, are characterized by a truncation of the intracellular tail, and lack the intracellular catalytic domain (Fenner 2012; Ferrer et al. 1999; Stoilov et al. 2002). In contrast to TrkB-T1, TrkB-T-Shc still contains the shc-binding site in the juxtamembrane region (see also chapter proteolytic truncation of TrkB in AD) (Stoilov et al. 2002). While activation of full length TrkB is mainly associated with neuroprotection and synaptic plasticity, the truncated isoforms are described as dominant negative regulators of full length TrkB. Alterations in the relative ratio of truncated TrkB receptors to full length TrkB may tilt the balance between neuroprotective and neurotoxic effects in AD (Allen et al. 1999; Wong et al. 2012a).

Proteolytic truncation of TrkB in AD

In addition to alternative splicing of TrkB, proteolytic truncation of the receptor was also suggested to be involved in the pathophysiology of Alzheimer's disease (Jeronimo-Santos et al. 2015; Xia et al. 2020). δ-Secretase, which facilitates the shift from nonamyloidogenic processing to the amyloidogenic pathway for APP (Zhang et al. 2015b, 2020), cuts the full length TrkB receptor intracellularly upstream of the shc-binding site as well as at extracellular residues, thereby inducing neurotoxicity (Figure 2) (Xia et al. 2020). Cleavage of TrkB as well as APP by δ-secretase was diminished after translocation of both receptors into the TGN via early endosomes and this translocation was controlled by TrkB-induced phosphorylation of APP (Xia et al. 2020). The interaction of TrkB and APP at the cell surface was shown to be dependent on the intracellular TrkB catalytic domain as well as on the intracellular domain of APP (Figure 5, Table 1) (Xia et al. 2020). The association of TrkB and APP at the surface membrane was characterized to be BDNF-independent and was also reduced in human AD brains (Xia et al. 2020). However, BDNF-induced TrkB activation was essential for phosphorylation of APP and translocation of the protein to the TGN (Xia et al. 2020).

In addition to δ-secretase, the Ca^{2+}-dependent protease calpain was shown to induce truncation of full-length TrkB downstream of the shc-binding site in an Aβ-dependent manner (Figures 2 and 4) (Jeronimo-Santos et al. 2015). Activation of calpain and cleavage of the TrkB receptor could be prevented by the NDMA receptor antagonist memantine (Tanqueiro et al. 2018) which is a drug used to treat Alzheimer's disease (Matsunaga et al. 2018). In line with this, NMDA receptor-dependent excitotoxicity was also efficient to stimulate TrkB cleavage by calpain (Figure 4) (Tejeda et al. 2016). For TrkBICD cleaved by calpain, accumulation of the fragments in the nucleus and phosphorylation of nuclear as well as cytosolic proteins have been demonstrated (Fonseca-Gomes et al. 2019).

Besides calpain cleavage, regulated intramembrane proteolysis (RIP) of TrkB receptor has been shown to be initiated by NMDA excitotoxicity. Shedding of full-length TrkB as well as the TrkB-T1 ectodomain by an unknown metalloproteinase (MMP) (see also chapter ADAM10) followed by γ-secretase cleavage of the intracellular domain of both isoforms could be demonstrated in primary cortical cultures (Figure 2) (Tejeda et al. 2016). The shedded ectodomain of TrkB was associated with reduced BDNF signaling due to scavenging of BDNF from extracellular space. However, function of the γ-secretase cleaved-intracellular domain of full length TrkB or TrkB-T1 is still unknown. Direct transcriptional regulation of gene expression could be one of the possible functions of the intracellular fragments (Chen et al. 2015; Lal and Caplan 2011).

Indirect transcriptional regulation of APP gene expression has been already shown to depend on full-length TrkB receptor activation by exogenous BDNF in SH-SY5Y cells (Ruiz-Leon and Pascual 2001). Furthermore, BDNF application stimulated APP promoter activity in TrkB-expressing SH-SY5Y cells (Ruiz-Leon and Pascual 2003) thereby strengthening the non-amyloidogenic pathway by enhancing the production of sAPPα (Ansaloni et al. 2011; Holback et al. 2005). However, so far, it is unknown whether BDNF rescues TrkB from proteolytic cleavage within the intracellular domain, thereby mediating gene expression by cytosolic signaling molecules and promoting neuroprotective functions of TrkB.

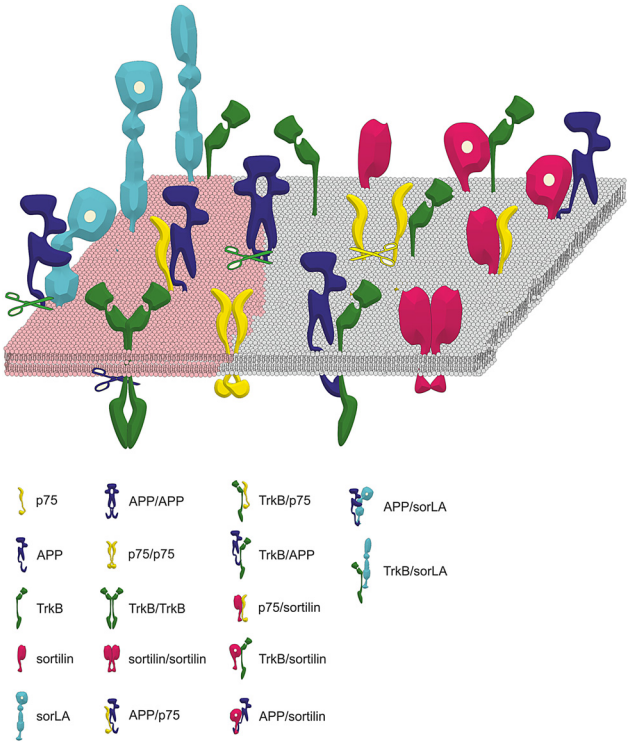

Figure 5: Protein-protein interactions of the different receptors on the cell surface.
Interactions of the different receptors have been demonstrated. TrkB receptor is known to form homodimers, but also heterodimerization of TrkB with p75, APP, sorLA and sortilin, respectively, have been reported. Intracellular TrkB catalytic domain as well as intracellular domain of APP are important for interactions of TrkB and APP at cell surface. These interactions are independent on the presence of BDNF. Interactions of sortilin and TrkB are responsible for anterograde transport of the receptor, while sorLA binds to TrkB at the cell surface and promotes internalization of the activated TrkB. Interaction of TrkB and p75 is suggested to require BDNF-induced TrkB activation followed by dynamin-mediated endocytosis. For APP, homodimerization as well as heterodimerization with p75, TrkB, sorLA and sortilin is known. Interaction of p75 and APP are reduced in the presence of neurotrophins and Aβ, respectively, indicating competing binding sites for the respective ligands. APP interacts further with sorLA and sortilin, respectively, via the intracellular region as well as via the ectodomain. In addition, the neurotrophin receptor p75 interacts with its coreceptor sortilin. Homodimerization of p75 and sortilin, respectively, has also been demonstrated. Only for sorLA, homodimerization could not be demonstrated. While sorLA seems to be predominantly located in cholesterol- and sphingomyelin rich lipid raft domains (membrane stained in rose), sortilin is more efficiently sorted to non-rafts domains (membrane stained in grey). TrkB translocates from non-raft to lipid raft domains after BDNF-binding. Recruitment of p75 to lipid rafts seems to be also dependent on ligand binding. In general, however, localization of the mentioned receptors to lipid raft or non-raft regions is not well understood. Distribution of p75/sortilin heterodimers or TrkB/sortilin heterodimer can only be speculated due to the predominant localization of sortilin to non-rafts.

p75 receptor: general aspects

The p75 neurotrophin receptor belongs to the tumor necrosis factor receptor superfamily. Binding of mature BDNF as well as proBDNF to the p75 receptor has been described. It is proposed that mature BDNF binds to p75/TrkB heterodimers while proBDNF has a higher binding affinity to the p75/sortilin complex (Meeker and Williams 2015). Full-length p75 consists of extracellular cysteine-rich domains, an intracellular juxtamembrane chopper domain and an intracellular C-terminal death domain (Figure 2) (Lin et al. 2015; Skeldal et al. 2011; Yuan et al. 2019). Neuroprotective as well as neurotoxic activities have been associated with BDNF- and proBDNF-dependent activation of p75 (Ibanez and Simi 2012).

Interactions of p75 with APP and its cleavage products

In addition to BDNF-signaling through p75, this neurotrophin receptor has been shown to interact with APP, sAPPα, sAPPβ, and Aβ, respectively, thereby inducing either neuroprotective or neurotoxic function (Figure 3, Table 1) (Costantini et al. 2005; Fombonne et al. 2009; Hasebe et al. 2013; Saadipour et al. 2018; Yao et al. 2015; Yi et al. 2021). Interactions of p75 and APP were partially reduced in the presence of neurotrophins and Aβ, respectively, indicating competing binding sites for the respective ligands (Fombonne et al. 2009). Furthermore, α-secretase mediated cleavage of APP was reduced in the presence of p75, while γ-secretase cleavage of β-CTF was increased under the same conditions, leading to enhanced cell death in neuroblastoma cells via caspase-3 activation (Fombonne et al. 2009). This is in line with observations from Saadipour et al., showing enhanced internalization of APP and β-secretase in the presence of p75 and Aβ, respectively (Saadipour et al. 2018). Aβ itself has also been shown to interact with p75 receptor, thereby inducing neurotoxicity (Knowles et al. 2009; Perini et al. 2002; Yaar et al. 2002) via the intracellular death domain (Perini et al. 2002). In contrast, neuronal viability was significantly enhanced due to reduced internalization and sorting of APP/p75 complex to β-secretase containing compartments in cultures of 5xFAD mice lacking death domain of p75 (Yi et al. 2021). In line, sAPPα has been shown to bind to p75 ectodomain, thereby inducing neurite outgrowth in cortical neurons (Hasebe 2013).

Proteolytic truncation of p75 in AD

Just like TrkB, p75 can be truncated by different proteases within the extracellular and intracellular domain (Bronfman 2007) and is processed in a similar manner as APP (Figure 2). Shedding of p75, by the α-secretases ADAM17 or ADAM 10 lead to the generation of a soluble 55 kDa ectodomain (p75ECD) and a membrane-bound C-terminal fragment (p75CTF) (Bao et al. 2018; Kanning et al. 2003; Zampieri et al. 2005) (see also chapter ADAM10). This shedding event was dependent on BDNF-induced TrkB activation (Ceni et al. 2010). Predominant localization of full length p75 at the plasma membrane indicates ectodomain shedding at the surface of the cell (Sykes et al. 2012). The soluble ECD of p75 was shown to contribute to cellular protection (Fang et al. 2020; Wang et al. 2011; Yao et al. 2015) by reducing β-secretase cleavage of APP (Yao 2015) and was significantly reduced in CSF and brains of AD patients (Jiao et al. 2015; Yao et al. 2015), while full length p75 increased Aβ production by ceramid-dependent activation of β-secretase.

Cleavage of p75 by α-secretase precedes cleavage of the intracellular domain (p75ICD) by γ-secretase (Frade 2005; Kanning et al. 2003; Urra et al. 2007), leading to the release of a cytosolic soluble ICD of p75 and the generation of a short transmembrane fragment (Kanning et al. 2003; Urra et al. 2007; Saadipour et al. 2017). While this short transmembrane region of the receptor specifically increased activation of TrkB at surface membrane (Saadipour et al. 2017) thereby potentially contributing to neuroprotection, the p75ICD is suggested to be associated with both neurotoxicity (Pathak et al. 2018; Kenchappa et al. 2006) and neuroprotection (Ceni et al. 2010; Matusica et al. 2013). Cleavage of p75ICD by γ-secretase was significantly diminished in the presence of TrkB receptor (Kanning et al. 2003) indicating differential cleavage pattern of p75 that depend on TrkB receptor availability. Although soluble p75ICD was often described as unstable, there is also evidence that p75ICD translocates into the nucleus in a BDNF and proBDNF-dependent manner (see also chapter sortilin) (Fleitas et al. 2018; Frade 2005; Pathak and Carter 2017; Kenchappa et al. 2006; Parkhurst et al. 2010). Furthermore, proBDNF modified by ROS-derived advanced glycation end products, which was significantly increased in CSF and brains of AD patients, also induced the translocation of p75ICD into the nucleus thereby mediating neurotoxicity (Fleitas et al. 2018).

Subcellular localization of p75 in AD

In addition to the importance of proteolytic processing of p75 receptor, subcellular localization of the receptor influences its signaling. Full length p75 is present in lipid rafts as well as in non-raft regions (Gil et al. 2007; Yu et al. 2004). Receptor surface diffusion was described to depend on cholesterol level in the plasma membrane with highest diffusibility of p75 in cholesterol-depleted conditions (Marchetti et al. 2019). Proteolytic p75CTF was absent in lipid rafts and cholesterol depletion results in increased shedding of p75NTR (Gil et al. 2007). Furthermore, proBDNF-induced apoptotic signaling via p75 receptor was abolished in cholesterol depleted conditions while mutated p75 characterized by a reduced localization in lipid rafts was only able to mediate proBDNF-induced apoptosis after cholesterol administration in cortical neurons (Marchetti et al. 2019). However, it must be pointed out, that cholesterol on its own influences receptor function.

Sortilin: general aspects

Sortilin (Sort1, neurotensin receptor3, gp95) is a type I transmembrane protein which functions as an endocytosis receptor and plays a role in protein sorting as well as cell signaling (Eggert et al. 2018b). The ectodomain of sortilin is mainly formed by the Vps10p domain, which consists of three domains: a ten-bladed β-propeller and two 10CC domains (10CC-a and 10CC-b) that were shown to interact with the β-propeller (Quistgaard et al. 2009) (Figure 2).

In general, sortilin is located predominantly in the TGN and cycles between endosomes and TGN similarly as sorLA (Gustafsen et al. 2013). It is trafficked via the secretory pathway and might transport ligands anterogradely (Gustafsen et al. 2013). After reaching the plasma membrane, predominantly in non-lipid rafts (Yang et al. 2013), sortilin is internalized and the receptor can further direct cargo to late endosomal compartments and to lysosomes for degradation (Nielsen et al. 1999). Sortilin itself is synthesized as an inactive precursor which is cleaved by the protease Furin to remove a 44 aa propeptide resulting in the mature form of the receptor (Munck Petersen et al. 1999). Furthermore, the metalloproteinases ADAM10 and ADAM17 process sortilin in the juxtamembrane region, leading to shedding of its extracellular domain from the cell surface (Evans et al. 2011; Hermey et al. 2006; Navarro

et al. 2002) (see also chapter ADAM10). Sortilin can also subsequently be cleaved by γ-secretase (Figure 2) (Nyborg et al. 2006; Hermey et al. 2006).

Sortilin and APP function

Sortilin full length protein levels as well as CTFs were found to be significantly increased in brains of AD patients (Finan et al. 2011; Fleitas et al. 2018; Saadipour et al. 2017). This is in line with the findings that sortilin is an important regulator of amyloidogenic APP processing. Sortilin overexpression increased BACE1 cleavage of APP thereby elevating Aβ production (Finan et al. 2011; Saadipour et al. 2017). However, results from two studies demonstrated increased amyloid plaque pathology in two different AD mouse models crossed with sortilin KO mice (Carlo et al. 2013; Ruan et al. 2018). Furthermore, Gustafsen et al. (2013), demonstrated that overexpression of sortilin results in increased sAPPα and decreased sAPPβ production.

Besides modulation of APP processing, sortilin functions as a neuronal receptor for APP and its cleavage products sAPPα and Aβ (Gustafsen et al. 2013; Takamura et al. 2012; Yang et al. 2013). Sortilin interacts with APP via the intracellular region as well as via the ectodomain (Figure 5, Table 1) (Yang et al. 2013). The binding site in the APP ectodomain was mapped to amino acids 1–141 within the growth factor-like domain (GFLD) which is part of the E1 domain. A different report mapped the APP-sortilin interaction site further distal to the E1 domain within the APP ectodomain (Gustafsen et al. 2013). In addition to APP, oligomerized Aβ has also been shown to bind sortilin, thereby inducing endocytosis of Aβ as well as apoptosis (Takamura et al. 2012).

For sAPPα, sortilin-dependent binding as well as internalization into different intracellular compartments has been shown (Gustafsen et al. 2013). The extracellular domain of APP was reported to interact with sortilin in a pH dependent manner with higher ligand-binding affinity at neutral pH and inhibition at an acidic pH, supporting the assumption that sAPPα binds sortilin at the cell surface (Gustafsen et al. 2013). In contrast, homo-dimerization of sortilin has been shown to depend on an acidic pH value (Figure 5, Table 1) and sortilin dimer formation in turn leads to the release of bound ligands in endosomes (Januliene et al. 2017; Leloup et al. 2017). Indeed, earlier studies have already demonstrated that interaction of sortilin with several such as the receptor associated protein (RAP) is lost at acidic pH (Munck Petersen et al. 1999). It was also suggested that sortilin homodimerization promotes its trafficking to the TGN and to extracellular vesicles (Itoh et al. 2018).

Sortilin and BDNF-signaling

It has been proposed that proneurotrophins (proNT) released by neurons and glial cells potentiate cellular apoptosis, thereby contributing to the marked loss of neurons in brains of AD patients (Fahnestock et al. 2001). An increased release of proNT plays a significant role in neuronal death involving receptor-mediated apoptosis (Gibon and Barker 2017; Glerup et al. 2014). In this context, sortilin is an essential component for transmitting pro-neurotrophin–dependent death signals from p75NTR (Jansen et al. 2007; Lewin and Nykjaer 2014; Nykjaer et al. 2004; Teng et al. 2005). In the death receptor complex, sortilin binds the pro-domain of pro-neurotrophins with high affinity forming a receptor complex with p75 that initiates apoptotic signaling (Nykjaer et al. 2004; Rogers et al. 2010) (Figure 3).

The mechanism by which sortilin and p75NTR transmit the apoptotic signal into cells is not completely understood, but involves JNK phosphorylation and the γ-secretase dependent release of the intracellular domain (ICD) of p75NTR, followed by nuclear translocation of the DNA-binding protein neurotrophin receptor inducing factor (NRIF) (Fleitas et al. 2018; Kenchappa et al. 2006; Volosin et al. 2006). The interaction of sortilin with p75NTR induces neuronal apoptosis, presumably increasing AD severity (Skeldal et al. 2011). This assumption is underlined by the finding of increased protein levels of proBDNF as well as its co-receptor sortilin in brains from AD patients which are both key signaling components involved in pro-apoptotic effects (Fleitas et al. 2018). Immunohistochemical analyses of brain slices of AD patients revealed a significantly increased number of apoptotic cells positive for p75 and sortilin (Fleitas et al. 2018). Interestingly, a different study showed that Aβ42 oligomers enhanced sortilin gene and protein expression via p75NTR and RhoA signaling pathways, suggesting a potential physiological interaction of Aβ42, proneurotrophins, p75 and sortilin in Alzheimer's disease (Saadipour et al. 2013).

In contrast, sortilin is also known to bind neurotrophic factors, such as BDNF (Richner et al. 2019; Teng et al. 2005). Earlier reports indicated that expression of the soluble sortilin ectodomain results in an increase in constitutive release of BDNF relative to cells expressing full length sortilin (Chen et al. 2005). Both, sortilin as well as BDNF are transported to lysosomes where they are degraded. This

sortilin-dependent degradation was shown to depend on the C-terminus of sortilin (Evans et al. 2011).

Furthermore, sortilin has been reported to associate with TrkB receptors (Akil et al. 2011; Wilson et al. 2016), which promotes cell survival, differentiation, innervation and plasticity/effect cell survival in neuronal cells (Akil et al. 2011; Vaegter et al. 2011). Sortilin binds Trk receptors to facilitate their anterograde trafficking and enhances Trk survival signaling by neurotrophins (Vaegter et al. 2011).

Therefore, sortilin acts as a molecular switch either by interacting with p75NTR resulting in an apoptotic response or binding TrkB receptors to induce neurotrophic effects.

SorLa: general aspects

SorLA (LR11) is a type I transmembrane protein consisting of an N-terminal VPS10 domain, followed by a YWTD/EGF-like domain, and multiple LDL receptor/FN3 repeats in the ectodomain (Figure 2) (Eggert et al. 2018b). Evidence suggests that sorLA might act as an sAPPα receptor (Andersen et al. 2006; Gustafsen et al. 2013). APP as well as sAPPα bind sorLA (Figure 5, Table 1). The interaction domain in APP has been mapped to its carbohydrate (E2) domain and to the CR domains 5–8 of sorLA (Andersen et al. 2006; Mehmedbasic et al. 2015). Of note, sorLA also binds soluble Aβ via its VPS10P domain and targets it for lysosomal degradation (Caglayan et al. 2014). If sorLA also acts as a homodimer as demonstrated for p75 (Vilar et al. 2009) or sortilin (Leloup et al. 2017) is unknown so far.

Interestingly, sorLA itself is cleaved by the α-secretase ADAM17 (Guo et al. 2002; Hampe et al. 2000; Hermey et al. 2006; Tsukamoto et al. 2014) (see also chapter ADAM10), leading to ectodomain shedding as well as γ-secretase cleavage (Hermey et al. 2006; Nyborg et al. 2006), similar as for APP processing (Figure 2).

SorLa and APP function

A possible implication of sorLA in AD was suggested by the finding of reduced levels of shedded sorLA in CSF (Guo et al. 2012a; Ma et al. 2009) as well as of sorLA full-length protein in brains of AD patients (Dodson et al. 2006; Ma et al. 2009; Sager et al. 2007; Scherzer et al. 2004). This is in line with studies showing that sorLA knockout mice exhibit higher Aβ levels in the brain as compared to WT mice (Andersen et al. 2005; Dodson et al. 2008) while overexpression of sorLA is known to lead to decreased Aβ production (Andersen et al. 2006; Offe et al. 2006; Schmidt et al. 2007), which is neuroprotective.

The effect of sorLA on the proteolytic conversion of APP has been demonstrated to be based on the impact of sorLA on APP transport, since the route by which APP is trafficked determines by which enzymes APP is proteolytically converted. SorLA is mainly localized to the Golgi apparatus and endosomes while only a minor fraction is present at the plasma membrane (Burgert et al. 2013; Eggert et al. 2018b; Gustafsen et al. 2013). There, sorLA may be involved in segregating APP CTFs into lipid rafts and excluding APP FL protein from lipid raft domains (Yoon et al. 2007).

Various studies indicate that sorLA can promote APP trafficking from endosomes to the Golgi apparatus (Andersen et al. 2005; Fjorback et al. 2012), or from endosomes to the cell surface (Huang et al. 2016), thereby preventing BACE1 cleavage of APP and Aβ production in acidified endosomes. According to this, co-expression of sorLA and APP led to a significant decrease of stationary vesicles and anterograde vesicles with a concomitant marked increase in the number of retrograde vesicles in primary cortical mouse neurons, suggesting that sorLA is mainly implicated in retrograde transport of APP (Eggert et al. 2018a).

The aforementioned data suggest that sorLA acts as a neuronal receptor. There is evidence that sAPPα down-regulates cyclin dependent kinase (CDK) 5 activity by binding to the sorLA receptor, which is essential to exert the trophic functions of sAPPα in neurons (Hartl et al. 2013). Interestingly, the sAPPα-sorLA interaction increased expression of hypoxia up-regulated protein 1 (ORP150) as effector protein which potentially mediates neuroprotective functions of sAPPα, thereby functioning as a protective chaperone (Hartl et al. 2013).

SorLA and BDNF-signaling

SorLA protein expression is significantly reduced in BDNF KO mice (Rohe et al. 2009). Furthermore, application of BDNF increases sorLA protein levels and thereby inhibits Aβ production in WT but not in sorLA KO neurons (Rohe et al. 2009). Therefore, the impact of BDNF on APP processing in regard to reduced Aβ production, seems to be mediated via sorLA, supporting the idea of a neuroprotective function of sorLA.

A different study demonstrated that sorLA interacts with TrkB (Figure 5, Table 1) and that loss of sorLA leads to an accumulation of TrkB at the cell surface (Rohe et al. 2013). Interaction with sorLA controls trafficking and synaptic exposure of TrkB since both, anterograde and retrograde transport of TrkB-eGFP containing vesicles was

impaired in sorLA KO neurons. Additionally, treatment of sorLA KO neurons with BDNF results in significantly reduced phosphorylation of TrkB, ERK, and Akt compared to WT neurons (Rohe et al. 2013). These data support a concept, where interaction with sorLA facilitates neuritic transport of TrkB to and from the synapse, thereby promoting BDNF signal transduction (Rohe et al. 2013).

ADAM10

A disintegrin and metalloproteinase 10 (ADAM10) has been identified as the major α-secretase acting on APP in neurons (Jorissen et al. 2010; Kuhn et al. 2010) and has proven its neuroprotective role in AD model mice by a reconstitution of behavioral deficits (Postina et al. 2004). In addition, ADAM17, also designated TACE, can exert α-secretase activity (Buxbaum et al. 1998; Endres et al. 2005; Slack et al. 2001). Interestingly, both proteases have been identified as participating in neurotrophin receptor cleavage: p75 and TrkA have been demonstrated to be shedded by ADAM17 as well as ADAM10 (Bao et al. 2018; Diaz-Rodriguez et al. 2002; Forsyth et al. 2014; Weskamp et al. 2004) and TrkB has been found to be processed due to excitotoxicity (Figure 2) (Tejeda et al. 2016). The protease involved in the latter regulatory scenario has not been identified yet. However, as ADAM10 is inducible by NMDA receptor activity, by calcium influx into the cell, or by glutamate (Guo et al. 2012b; Nagano et al. 2004; Sakry et al. 2014; Suzuki et al. 2012), it is appealing to speculate about the enzymes involvement in cleavage of TrkB. This shedding results in a soluble receptor ectodomain that scavenges BDNF within the extracellular space (Tejeda et al. 2016), and would not allow it, executing its neurotrophic function via cell-bound receptors. Contrarily, to this impairing function of ADAM10 on BDNF, the protease also might positively act on the factors' bioavailability. ADAM10 was identified as the preferred protease cleaving sortilin (Figure 2) (Evans et al. 2011). The expression of the respective sortilin ectodomain released by this processing prevents BDNF translocation to the lysosomal department and its subsequent degradation (Chen et al. 2005).

The interaction between the α-secretase and BDNF seems also to be mutual: at least in the context of retinoic acid signaling, BDNF has been shown to augment activity of the α-secretase, resulting in elevated release of sAPPα (Holback et al. 2005; Nigam et al. 2017). Such a co-regulation has also been described for restoration of retinoic acid supply to SH-SY5Y cells (Reinhardt et al. 2016), where ADAM10 and BDNF expression both were increased. More recently, an increase of BDNF could also be observed in AD model mice treated with the synthetic retinoid acitretin (Rosales Jubal et al. 2021). Not only did the treatment rebalance excitatory synapses in the visual cortex, it also increased the amount of BDNF.

Conclusions and future directions

Alzheimer's disease is characterized by a slow progression of cognitive decline and preclinical symptoms are evident up to 25 years before onset of the disease. One may ask whether cellular processes are really responsible for the outbreak of this disease or whether subtle dysregulations of interconnected networks rather lead to the massive brain disorder. Due to this lack of knowledge, it is also unknown if there exists a point of no return on progression of neuronal cell death or whether there is a time point at which the cognitive decline can be stopped and not just delayed. Regardless of the original cause of AD, dysregulations or disorders can be treated by drugs which mostly elicit their responses at cellular level. In addition, cellular changes and adaptive responses are ultimately the main cause of dysregulation at higher levels. The knowledge about the balance of this cellular functions as well as adaptive responses allows us to find medical or non-medical therapies to treat Alzheimer's disease maybe even before massive neuronal cell death occurs. Therefore, further studies will need to address the complexity of signaling pathways with all its properties like synergistic effects, feedforward and feedback loop, crosstalk as well as spatial and temporal dynamics. APP and BDNF signaling are described to be independent pathways which are linked via crosstalk and feedback mechanism e.g., on gene expression level. However, several common features concerning sorting and processing of BDNF receptors and APP strengthen a causal relationship of both signaling pathways:

- The balance of proBDNF/BDNF-signaling as well as the balance of sAPPα/Aβ cleavage significantly contributes to neuroprotective and neurotoxic functions. Quantification of protein ratios e.g. in brain tissue, CSF and blood samples of patients could be used as an indicator of early stages of the disease.
- Similar stimuli induce release of BDNF and also promote α-secretase-mediated cleavage of APP. However, whether both proteins can be co-released e.g. during LTP or learning and memory is unknown. Furthermore, common stimuli to induce BDNF and sAPPα release such as forskolin might function as a pharmacological drug.

- BDNF/TrkB signaling and sAPPα activate common intracellular signaling pathways e.g. during NMDA-dependent plasticity processes or neuroprotection. Whether both pathways are connected in parallel thereby converging on the same intracellular signaling molecules or whether these pathways are connected in series (e.g. by translocation of the respective receptors) is unknown.
- Aβ and BDNF negatively influence expression and processing of each other. In addition, transport of BDNF is affected by Aβ, thereby potentially balancing plasticity processes and neuronal excitotoxicity.
- p75 receptor exhibits binding capacity to BDNF and its signaling partners as well as to APP and its cleavage products, respectively, therefore making this receptor suitable to bridge or even to combine both pathways.
- APP, TrkB, p75, sorLa and sortilin directly interact with each other. Whether the receptors heteromultimerize needs to be clarified by protein-protein interaction studies. Pharmacological drugs which inhibit specific protein-protein interactions like p75 and full length APP could be a new therapeutical approach.
- Proteolytic cleavage of TrkB, p75, APP, sorLa and sortilin share common features. It is unknown whether cutting of receptors takes place simultaneously in the di- or multimeric complex. Analysis of soluble protein fragments as well as quantification of protein ratios in brain tissue, CSF and blood samples of patients might help to reveal molecular characteristics of AD thereby potentially uncovering new biomarkers of the disease.
- SorLA and sortilin are likely to separate lipid raft from non-raft signaling routes of APP, TrkB and p75, respectively, thereby influencing aspects of sorting as well as the degree of intracellular enzyme activation or inhibition.

Future research will reveal the impact of BDNF and APP interplay as well as interactions with the other signaling partners in AD diagnosis and therapy.

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