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Chapter 7

Neurotrophin Signaling and Alzheimer's Disease Neurodegeneration – Focus on BDNF/TrkB Signaling

Jenny Wong

Additional information is available at the end of the chapter

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1. Introduction

1.1. Neurotrophins

Neurotrophins are small proteins vital for neuronal growth, differentiation, survival, and plasticity [1]. Members of the mammalian neurotrophin family include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). Their neurotrophic effects are mediated by the tropomyosin receptor kinase (Trk) receptors, membrane-bound receptor tyrosine kinases (NGF for TrkA, BDNF and NT4/5 for TrkB, and NT-3 for TrkC) which activate various cell signaling pathways linked to growth, differentiation, and survival [2]. The importance of neurotrophin signaling in brain development is highlighted by findings showing that knockout mice for any one of the neurotrophins or their receptors are fatal or exhibit severe neural defects [3].

1.2. BDNF and Alzheimer's disease

The neurotrophin, NGF, is reduced in the nucleus basalis, a region concentrated in basal forebrain cholinergic neurons, which show substantial degeneration in Alzheimer's disease (AD) [4, 5]. However, there is conflicting evidence demonstrating that NGF levels are unchanged or even increased in other brain regions including the frontal cortex and hippocampus, two major brain regions affected in AD [6-9]. In contrast, BDNF is more highly expressed and widely distributed in the brain compared to NGF, and its expression and growth promoting actions are critical for survival and plasticity of a variety of neurons throughout the brain, particularly in brain regions heavily affected in AD such as hippocampal, cortical, and cholinergic neurons [10-14]. Moreover, in cell culture and animal models, functioning of the BDNF signaling pathway has been repeatedly demonstrated to be critical for neuronal differentiation, survival, plasticity, and cognition [3, 11, 13, 15-21]. Independent

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lines of evidence suggest that dysfunction in BDNF signaling may contribute to the neurodegeneration in AD. Brain regions associated with reduced BDNF expression are those displaying the highest levels of neurodegeneration (eg. hippocampus). The role of BDNF in AD has been studied extensively. In AD brains, BDNF mRNA and protein levels have been found to be reduced in the hippocampus and neocortex [8, 22-27]. With findings of reduced BDNF expression in AD, interest emerged in the role of the TrkB receptor, as reductions in BDNF signaling may also occur through alterations in and/or through decreased expression of this BDNF receptor.

1.3. The BDNF receptor – TrkB

The TrkB receptor is the principal component of the BDNF signaling pathway. In the human brain, multiple isoforms of TrkB are expressed. There are three major isoforms of the TrkB receptor characterized to date: the full-length (TrkB-TK+) and two C-terminal truncated TrkB receptors (TrkB-TK- and TrkB-Shc) that are generated by alternative splicing of the TrkB pre-mRNA [28]. The full-length TrkB receptor, TrkB-TK+, is the principal mediator of the neurotrophic effects of BDNF. Upon ligand binding, monomeric TrkB-TK+ homodimerizes and undergoes trans-phosphorylation at key tyrosine residues in the C-terminal domain that couple it to downstream signaling pathways that promote neuronal survival, growth, differentiation, and plasticity including mitogen-activated protein kinase kinase (MEK), phosphatidyl inositol 3 kinase (PI3K), and phospholipase C-gamma (PLCγ) [29-32] (Figure 1). The two truncated TrkB receptor isoforms include TrkB-TK- and TrkB-Shc. Both truncated isoforms are generated from alternatively spliced transcripts and are truncated at the C-terminus, thus lacking the tyrosine kinase domain [28, 33]. However, the TrkB-TK- and TrkB-Shc receptors differ in that each contain unique amino acid sequences at their C-terminus. The TrkB-Shc isoform includes the sarc homology containing (Shc) binding domain that is absent in TrkB-TK- [28].

1.4. TrkB and Alzheimer's disease

Previous reports on TrkB-TK+ and TrkB-TK- expression levels in AD have been variable due to brain cohort differences and the variable techniques used to measure their expression. In general, reductions in TrkB-TK+ in neurons have mostly been found in the hippocampus and the frontal and temporal cortices in AD [27, 34]. Conversely, up-regulation of TrkB-TK- has been found in association with senile plaques in AD, and is suggested to be linked to increases in reactive glial cells [9, 27, 34]. Furthermore, increases in TrkB-TK+ have also been found in glial cells in the hippocampus [27]. Surprisingly, while the existence of TrkB-Shc has been known for some time, its role in AD has not been defined.

1.5. Importance of TrkB

Neuron viability and function is dependent upon BDNF-stimulated TrkB-TK+ signaling. In AD, much evidence suggests that BDNF/TrkB-TK+ signaling is reduced [8, 22-27, 34-36]. In addition to changes in BDNF expression, neuronal BDNF/TrkB-TK+ signaling can also be modulated by alterations in the ratio of full-length (TrkB-TK+) to truncated (TrkB-TK- and

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TrkB-Shc) TrkB expressed [31, 37]. Homodimers of TrkB-TK+ receptors bind to BDNF and initiates intracellular second messenger signaling (Figure 1). Changes in TrkB alternative transcript expression or protein stability, such as increased TrkB-TK- and/or TrkB-Shc, will have a profound negative impact on BDNF/TrkB-TK+ signaling as homodimers of truncated receptors and heterodimers of full-length and truncated receptors can not initiate BDNF-stimulated second messenger signaling (Figure 2). This is important because changes in the ratio of full-length to truncated TrkB expression in neurons may underlie reductions in neurotrophic support in AD, which ultimately lead to neurodegeneration and profound neuron and brain volume loss. Considering that TrkB-Shc is a brain- and neuron-specific TrkB isoform that has been demonstrated to inhibit BDNF/TrkB-TK+ signaling, it is important to establish what role TrkB-Shc plays in AD development and progression.

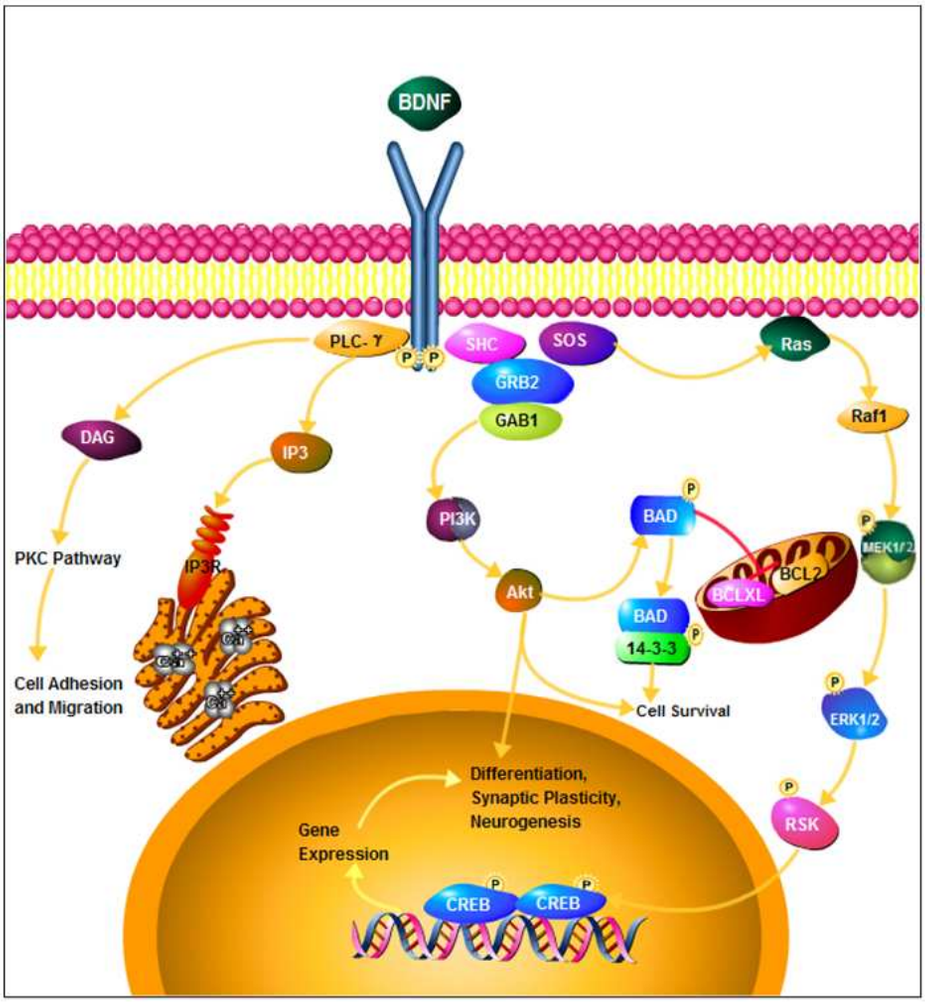


Figure 1. BDNF/TrkB-TK+ signaling pathway. Activation of TrkB-TK+ by BDNF leads to auto-phosphorylation of tyrosine residues in the intracellular C-terminal domain. This leads to the activation of TrkB-TK+-linked second messenger signaling pathways including PLCγ (phospholipase C-gamma), MEK (mitogen-activated protein kinase kinase), and PI3K (phosphatidyl inositol 3 kinase), which are linked to downstream processes involved in cell adhesion/migration, cells survival, synaptic plasticity, neurogenesis, and neuronal differentiation. This figure is modified from the BDNF Pathway Figure (Protein Lounge Pathway Templates) from ProteinLounge using Pathway Builder Tool.

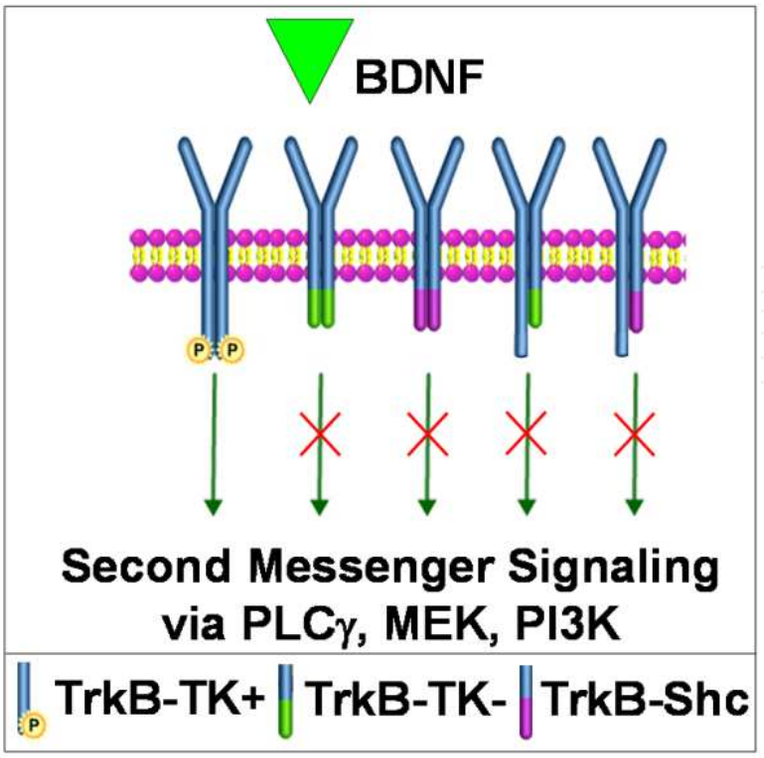


Figure 2. TrkB receptor dimer combinations. All dimer combinations of TrkB receptors can bind to BDNF. However, only a homodimer of TrkB-TK+ can initiate second messenger signaling. This figure utilizes modified ProteinLounge graphics created using the Pathway Builder Tool (www.proteinlounge.com).

2. Evidence that TrkB-Shc alternative transcripts are selectively increased in the hippocampus during severe, late stage AD

In Wong et al. (2012) [38], we measured changes in TrkB alternate transcript levels in control and AD postmortem human brain tissue derived from the hippocampus, temporal cortex, occipital cortex, and cerebellum (Braak stages V and VI) [38]. By quantitative real-time PCR, using primers specific for each TrkB alternative transcript, we found significant increases in TrkB-Shc mRNA expression in the hippocampus but not in any other brain region (Figure 3).

Considering that brain homogenates contain a mixed population of cells, we determined whether the changes found in TrkB transcript expression using the hippocampal tissue homogenates also occur in neurons exposed to an amyloidogenic environment. Here, changes in TrkB transcripts were assessed by incubating differentiated SHSY5Y cells (a human neuroblastoma cell-line which express TrkB) with different species of amyloid beta 1-42 ($A\beta_{42}$) peptides at various stages of aggregation. Oligomers and fibrils were prepared as described in Ryan et al. [39] and characterized by western blotting and atomic force microscopy imaging [38]. A significant increase in TrkB-Shc mRNA levels was found when cells were incubated with preparations of $A\beta_{42}$ containing fibrils compared to controls (Figure 4). The small magnitude of change was expected as the $A\beta_{42}$ fibril preparation contained mixed $A\beta_{42}$ spe-

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cies and the absolute amount of fibrils would be low (fibrils were absent in the monomer and oligomer $A\beta_{42}$ preparations). Further, in comparison to the $A\beta_{42}$ monomer and oligomer preparations, the $A\beta_{42}$ fibril preparations would be most representative of all $A\beta_{42}$ species present in the AD hippocampus as this preparation comprises a mix of all three species [38]. These results were consistent with findings of increased TrkB-Shc mRNA levels in the AD hippocampus (Figures 3 and 4).

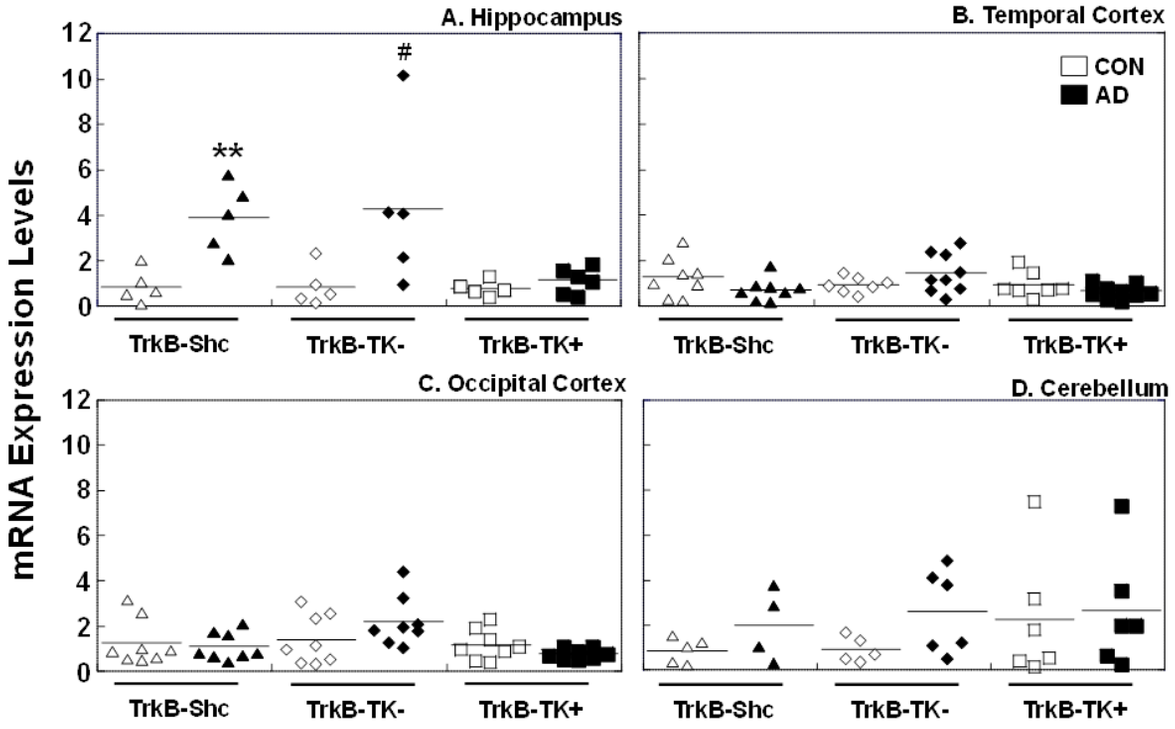


Figure 3. TrkB alternative transcript expression in various control and AD brain regions. Expression of TrkB alternative transcripts in the (A) hippocampus, (B) temporal cortex, (C) occipital cortex, and (D) cerebellum of control (CON) (white) and Alzheimer's disease (AD) (black) postmortem human brain tissue were measured by qPCR. ** P=0.004; # P=0.07. Figure is from Wong J, et al. Amyloid beta selectively modulates neuronal TrkB alternative transcript expression with implications for Alzheimer's disease. Neuroscience 2012;210 363-374.

In regards to the brain regions examined, AD brain pathology from most severe to least affected is: hippocampus>temporal cortex>occipital cortex>cerebellum. The selective increase in TrkB-Shc transcripts observed only in the hippocampus suggested that the elevated TrkB-Shc transcript levels were occurring in brain regions that are most severely affected in the diseased state and that the observed increase may likely be influenced by the neuronal cell population present. This was supported by our *in vitro* AD cell culture model showing that TrkB-Shc mRNA levels in the differentiated SHSY5Y neuronal cells can be increased by exposure to preparations of $A\beta_{42}$ containing fibrils. $A\beta_{42}$ fibril species are increased in the advanced stages of AD [40]. While it is widely accepted that soluble oligomers are the more neurotoxic of the $A\beta_{42}$ species, evidence also suggest that the neurotoxicity of $A\beta_{42}$ requires its aggregation in the fibrillar form, particularly in the form of protofibrils [41, 42]. In our $A\beta_{42}$ preparations, we detected various sizes of fibrils in the $A\beta_{42}$ fibril preparations, includ-

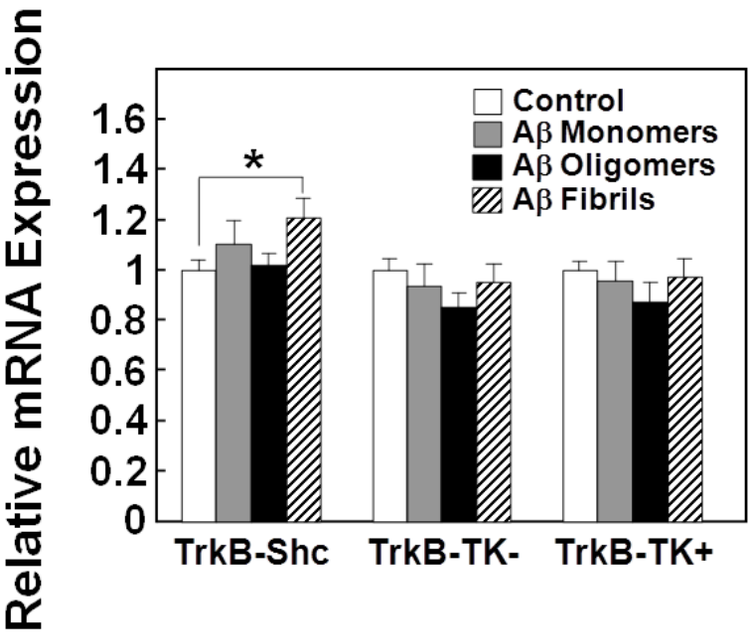


Figure 4. Effect of different structural forms of $A\beta_{42}$ on TrkB alternative transcript expression in differentiated SHSY5Y neuronal cells. SHSY5Y cells were differentiated for 9 d and incubated in the absence (white bars) or presence of 1 μM $A\beta_{42}$ monomers (AβM) (gray bars), oligomers (AβO) (black bars), and fibrils (AβF) (hatched bars) for 6 h and harvested. Expression of TrkB alternative transcripts were then measured by qPCR. Data are expressed as mean + SEM relative to the control (white bars) condition that was set to 1. * P=0.03. Figure is from Wong J, et al. Amyloid beta selectively modulates neuronal TrkB alternative transcript expression with implications for Alzheimer's disease. Neuroscience 2012;210 363-374.

ing protofibrils which can be ~100 nm in length. If we consider that $A\beta_{42}$ fibrils are predominant in the advanced stages of AD [40], that the hippocampus is the most affected brain region, and that the CA1 subregion (the hippocampal region assessed) is the most severely impacted subregion of the hippocampus in AD, altogether, our findings suggest that the selective increase in the TrkB-Shc alternative splice transcript in the AD hippocampus may be specific to severe, late stage pathology.

3. TrkB-Shc inhibits TrkB-TK+ function and BDNF/TrkB-TK+ signaling

The elevated levels of TrkB-Shc in AD suggested that it may have a functional impact on cellular TrkB-TK+ signaling *in vivo*. Previous studies have demonstrated that TrkB-Shc can function as a dominant negative receptor by inhibiting TrkB-TK+ phosphorylation [28]. In Wong et al. (2012) [38], we confirmed this finding and extended it by showing that TrkB-Shc can decrease downstream second messenger signaling linked to TrkB-TK+, supporting a dominant negative function of TrkB-Shc on BDNF/TrkB-TK+ signaling. In particular, we found that when TrkB-Shc was overexpressed in SHSY5Y cells (which express endogenous TrkB-TK+), BDNF/TrkB-TK+ stimulated MEK pathway signaling was selectively attenuated. The ratio of phosphorylated ERK1/2:total ERK1/2 (a measure of ERK1/2 activity) was re-

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duced but little change was observed for phosphorylated TrkB:total TrkB-TK+ and phosphorylated AKT:total AKT ratios (Figure 5).

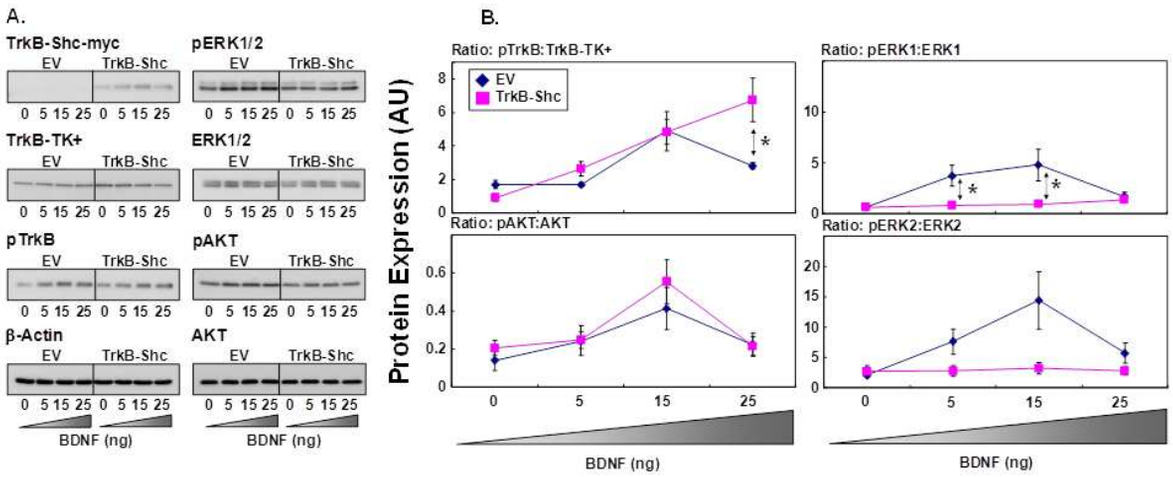


Figure 5. Effect of TrkB-Shc overexpression on BDNF-stimulated TrkB-TK+ second messenger signaling in differentiated SHSY5Y neuronal cells. Differentiated SHSY5Y cells were transfected with either empty vector (EV; blue) or myc-tagged TrkB-Shc (pink) for 24 h and treated with increasing concentrations of BDNF for 15 min and harvested. Proteins were separated by Western blotting and immunoprobed. (A) Representative Western blot images. (B) Bands were quantitated by densitometry and presented as protein expression ratios of phosphorylated protein to non-phosphorylated protein (pTrkB-TK+:TrkB-TK+; pAKT:AKT; pERK1:ERK1; pERK2:ERK2) -/+ SEM. * P=0.02 for pTrkB:TrkB-TK+ at 25 ng, P=0.03 for pERK1:ERK1 at 5 ng BDNF and P=0.049 for pERK1:ERK1 at 15 ng BDNF. Figure is from Wong J, et al. Amyloid beta selectively modulates neuronal TrkB alternative transcript expression with implications for Alzheimer's disease. Neuroscience 2012;210 363-374.

In a parallel study [43], we determined how TrkB-Shc exerts its dominant negative effect on BDNF-stimulated TrkB-TK+ signaling. Using a non-neuronal cell-line, Chinese Hamster Ovary K1 (CHOK1) cells (which do not express endogenous TrkB receptors), we transiently overexpressed TrkB-Shc protein and examined its effect on TrkB-TK+ protein stability. We used cycloheximide to block protein synthesis as this would prevent newly synthesized protein from replacing protein that has been degraded. From this, we found that TrkB-Shc protein levels were rapidly decreased when cells were exposed to exogenous BDNF. Moreover, in co-expression experiments where TrkB-Shc and TrkB-TK+ were co-expressed, cycloheximide treatment revealed increased protein degradation of phosphorylated TrkB-TK+ protein, a process that is accelerated by BDNF exposure (Figure 6A and B) [43]. Interestingly, while the reduction of phosphorylated TrkB-TK+ protein was more pronounced in the presence of TrkB-Shc following BDNF exposure, the stability of TrkB-Shc protein itself was increased (Figure 6C).

4. Discussion

Our recent findings have important implications in regards to the role of TrkB-Shc and its impact on BDNF-mediated TrkB-TK+ signaling in neurons in AD. MEK signaling through

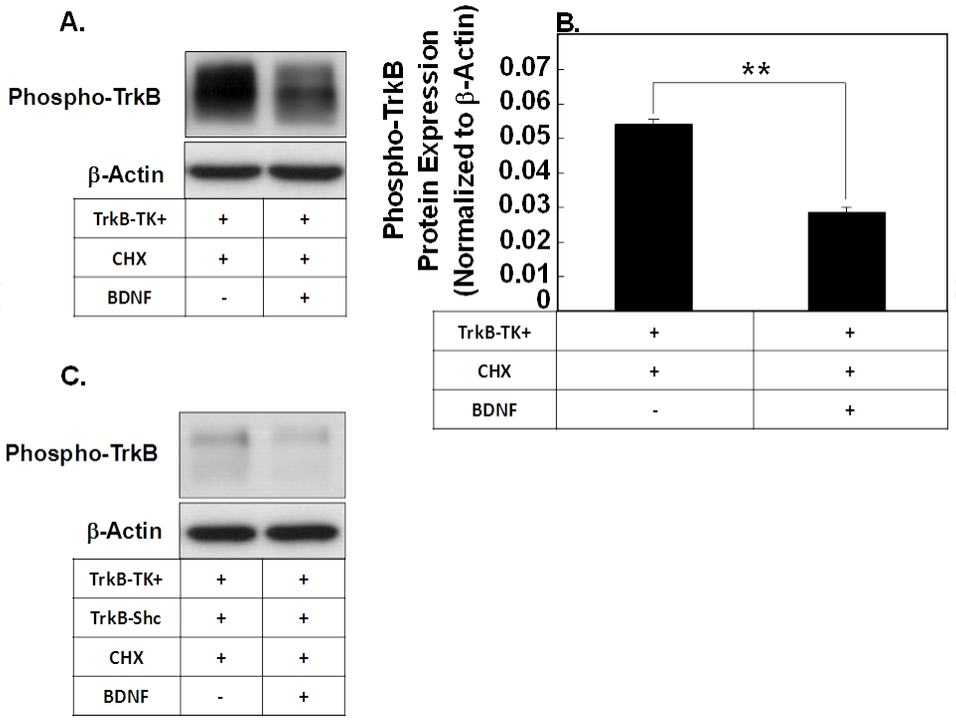


Figure 6. Effect of TrkB-Shc on the stability of phosphorylated TrkB-TK+. CHOK1 cells co-transfected with either empty vector + TrkB-TK+ or TrkB-TK+ + TrkB-Shc for 24 h were treated with 15 ng BDNF for 15 min and then incubated with cycloheximide for 3 h before harvest. Proteins were separated by Western blotting and immunoprobed. (A and C) Representative Western blot images. (A) and (C) are from the same blot and have the same exposure. (B) Bands in (A) were quantitated by densitometry and presented as protein expression normalized to β-actin + SEM. **P = 0.007. Figure is from Wong, J and Garner, B. Biochemical and Biophysical Research Communications 2012; 420 331–335.

ERK1/2 phosphorylation is increased in vulnerable neurons in AD and is implicated in the abnormal phosphorylation of tau and neurofilament proteins [44]. Our finding of a selective attenuation in MEK signaling activity in neurons with elevated levels of cellular TrkB-Shc implicates that elevated levels of this neuron-specific truncated TrkB receptor in AD may occur as a response to the disease. However, our finding that cells may increase TrkB-Shc protein levels in response to BDNF stimulation to regulate TrkB-TK+ activity by increasing degradation of activated receptor complexes also has ramifications for BDNF/TrkB-TK+ signaling in AD. In the non-diseased or control state, this process is akin to feedback regulatory loops observed in metabolic pathways (Figure 7). While BDNF/TrkB-TK+ signaling is important in multiple aspects related to neuronal viability and differentiation, overactivation or inappropriate temporal and spatial activation of BDNF/TrkB-TK+ signaling during brain development or "leakage" of BDNF to adjacent neurons or brain regions can negatively impact brain function. However, in AD, elevated levels of TrkB-Shc in association with reduced BDNF protein levels (which is well documented) and no change in TrkB-TK+ expression may also result in an overall increase in the degradation of phosphorylated TrkB-TK+ receptors, and thus, reduce overall BDNF/TrkB-TK+ activity in neurons in AD.

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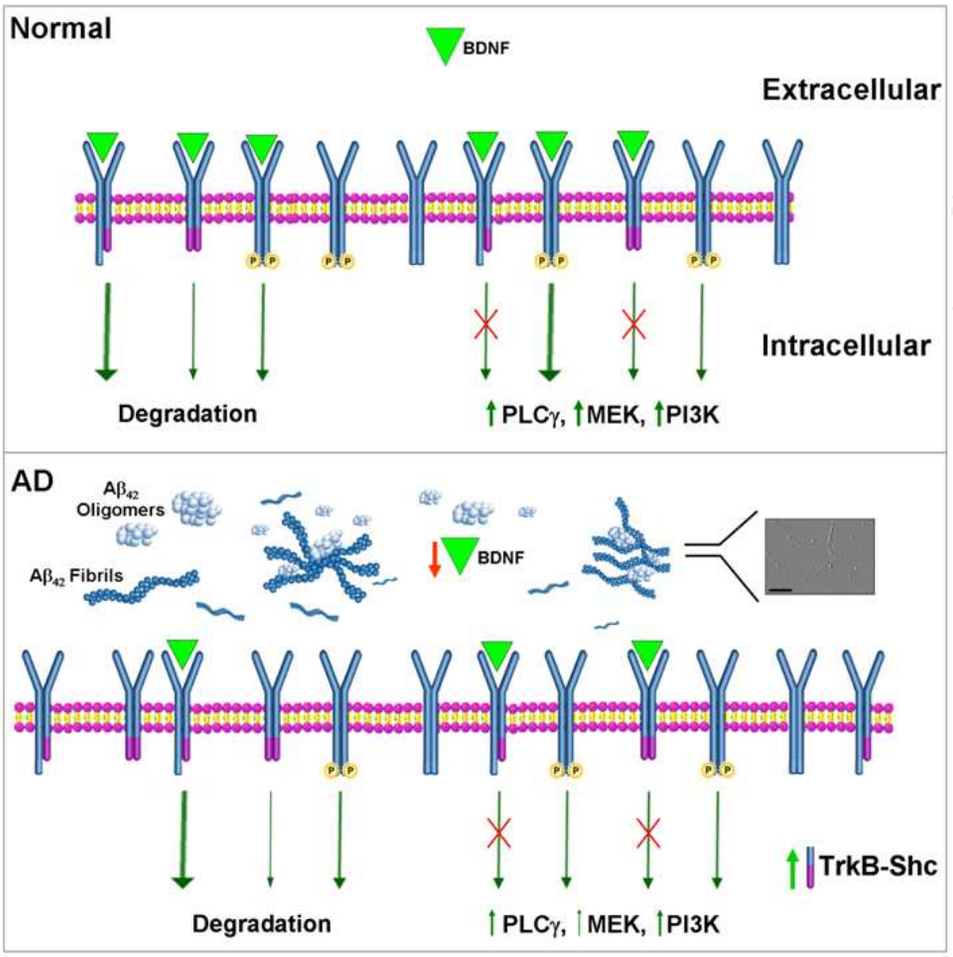


Figure 7. Summary diagram. Upper panel: In the normal, non-diseased state, binding of BDNF to TrkB leads to auto-phosphorylation of TrkB-TK+ homodimers (but not other TrkB dimer combinations). This leads to activation of downstream second messenger signaling pathways including PLCγ (phospholipase C-gamma), MEK (mitogen-activated protein kinase kinase), and PI3K (phosphatidyl inositol 3 kinase), which are critical for neuronal viability and function. TrkB-TK+ homodimers can also be auto-phosphorylated in the absence of BDNF, although activation of downstream signaling pathways are less intense. BDNF-stimulation of TrkB receptors also leads to their degradation. The arrow thickness indicates the magnitude of effect. The magnitude of decrease in protein levels are greatest for the following receptor combinations when stimulated with exogenous BDNF: TrkB-TK+/TrkB-Shc>TrkB-TK+/TrkB-TK+>TrkB-Shc/TrkB-Shc. Lower panel: In AD, there is Aβ plaque accumulation. Neurons are exposed to mixed species of Aβ, including $A\beta_{42}$ fibrils and oligomers at various stages of aggregation. BDNF protein expression has been reported to be reduced in AD (indicated by red arrow) and TrkB-Shc levels have been reported by us to be increased in AD (hippocampus, CA1) (indicated by green arrow) and in response to $A\beta_{42}$ fibril exposure. The increase in TrkB-Shc is predicted to increase heterodimer combinations of TrkB-TK+/TrkB-Shc and homodimer combinations of TrkB-Shc, which would lead to an overall reduction in downstream signaling. Moreover, the increase in TrkB-Shc dimer combinations also increases TrkB receptor degradation. Thus, the combination of reduced BDNF expression and increased TrkB-Shc expression in the AD hippocampus would likely result in an overall decrease in BDNF/TrkB-TK+ signaling. Figure utilizes modified ProteinLounge graphics created using the Pathway Builder Tool (www.proteinlounge.com). Insert panel: Atomic force microscopy image of the $A\beta_{42}$ fibril preparation used in Wong J, et al. Amyloid beta selectively modulates neuronal TrkB alternative transcript expression with implications for Alzheimer's disease. Neuroscience 2012;210 363-374. This contains mixed species of $A\beta_{42}$ monomers, oligomers, and fibrils of various sizes. Scale represents 1 μm.

5. Conclusion

Neurotrophin signaling via BDNF/TrkB-TK+ is critical for neuronal viability and function. Further research into this topic area is required to determine when changes in BDNF/TrkB-TK+ signaling begin to occur and whether changes in TrkB-Shc expression, function, and interaction with TrkB-TK+ at different stages of the disease process, in response to Aβ, or in response to other amyloidogenic factors may be protective or deleterious.

Nomenclature

Aβ (amyloid beta), AD (Alzheimer's disease), Akt (protein kinase B), BDNF (brain-derived neurotrophic factor), CA1 (Cornu Ammonis area 1), CHO (Chinese hamster ovary), ERK (extracellular signal-regulated kinase), MEK (mitogen-activated protein kinase kinase), NGF (nerve growth factor), NT (neurotrophin), PI3K (phosphatidyl inositol 3 kinase), PLCγ (phospholipase C-gamma), Shc (sarc homology containing), Trk (tropomyosin receptor kinase).

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Author details

Jenny Wong[1,2]

Address all correspondence to: jwong@uow.edu.au

1 Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, NSW, 2522, Australia

2 School of Biological Sciences, University of Wollongong, Wollongong, NSW, 2522, Australia

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