REVIEW

Regulation of TrkB cell surface expression—a mechanism for modulation of neuronal responsiveness to brain-derived neurotrophic factor

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Abstract

Neurotrophin signaling via receptor tyrosine kinases is essential for the development and function of the nervous system in vertebrates. TrkB activation and signaling show substantial differences to other receptor tyrosine kinases of the Trk family that mediate the responses to nerve growth factor and neurotrophin-3. Growing evidence suggests that TrkB cell surface expression is highly regulated and determines the sensitivity of neurons to brain-derived neurotrophic factor (BDNF). This translocation of TrkB depends on co-factors and modulators of cAMP levels, N-glycosylation, and receptor transactivation. This process can occur in very short time periods and the resulting rapid modulation of target cell sensitivity to BDNF could represent a mechanism for fine-tuning of synaptic plasticity and communication in complex neuronal networks. This review focuses on those modulatory mechanisms in neurons that regulate responsiveness to BDNF via control of TrkB surface expression.

Introduction

Nerve growth factor (NGF) was the first member of the neurotrophin family that was discovered as a survival factor for distinct populations of neurons during a critical period of development. When brain-derived neurotrophic factor (BDNF) and the other members of the neurotrophin family were identified, it became apparent that the responsiveness of BDNF-sensitive neurons was also qualitatively different from NGF-dependent neurons. These differences can be explained by differential target cell responsiveness to BDNF rather than differential expression of the corresponding TrkB receptor. In the present article, we aim to provide an overview about some historic aspects that first pointed to differences between NGF and BDNF, and recent findings on molecular mechanisms how target cell sensitivity to BDNF signaling is regulated by TrkB cell surface expression. These mechanisms could explain differential responsiveness of developing neurons to NGF and BDNF.

Work by Viktor Hamburger and others has shown that many types of neurons are generated in excess in the embryonic nervous system of vertebrates and that only subpopulations that are supported by neurotrophic factors are maintained (reviewed by Purves and Lichtman 1985a). In the peripheral nervous system, these neurotrophic factors have been proposed to be derived from innervated target areas (reviewed by Purves and Lichtman 1985a), based on observations such that limb bud elimination during this critical period enhances cell death (Hamburger 1934). At the same time, augmentation of target tissue by transplantation of a supernumerary limb reduces neuronal loss. This was the basis for the discovery of nerve growth factor (NGF), the first prototypical neurotrophic factor (reviewed by Lewin and Barde 1996, Purves and Lichtman 1985b). Neurotrophins mediate survival effects via specific transmembrane tyrosine kinase receptors of the Trk family, TrkA, TrkB, and TrkC (reviewed by Chao 2003; Huang and Reichardt 2003; Kaplan and Miller 2000). NGF is required for the survival of developing sensory and sympathetic neurons (Thoenen et al. 1981) but not spinal motoneurons.

Whereas the physiological actions of NGF on developing sympathetic and sensory neurons were confirmed by analyses of in vitro models and knockout mice (Crowley et al. 1994; Nikoletopoulou et al. 2010; Ruberti et al. 2000), the

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physiological action of BDNF on developing spinal motoneurons remained obscure and partially also controversial. While isolated early sensory ganglionic neurons from E8 chick embryos survive in the presence of NGF (Davies and Lindsay 1985; Edgar and Thoenen 1982; Thoenen et al. 1981), E6 chick spinal motoneurons can be maintained in cell culture only at low efficacy with BDNF (Arakawa et al. 1990). As a positive control, other neurotrophic factors such as CNTF appeared much more potent (Arakawa et al. 1990; Berkemeier et al. 1991). However, responsiveness to BDNF developed in cultures of embryonic chick motoneurons when these cells were primed with muscle extracts (Becker et al. 1998). Subsequent studies showed that it was not the absence of TrkB that was responsible for the low survival response of early embryonic chick motoneurons to BDNF. TrkB was abundantly expressed in early chick motoneurons and it appeared activated even in the absence of BDNF when these cells were treated with glial-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), or fibroblast growth factor (FGF) (Becker et al. 1998). This indicates that muscle extracts contain factors similar to CNTF or FGF that potentiate the response of developing motoneurons to BDNF. This could be interpreted as a differentiation effect that activates responsiveness to BDNF. Alternatively, and not exclusively, other growth factors also could transactivate TrkB (Castellino and Chao 1996; Lee and Chao 2001), and the survival-promoting effects of activated G protein–coupled receptors such as adenosine type 2A receptors (A_2A-R) depend on the presence of TrkB (Wiese et al. 2007). On the other hand, isolated rat or mouse motoneurons from E12 to E15 embryos survive with high efficacy in the presence of BDNF when cultured with enriched cell culture media (Hughes et al. 1993). Moreover, postnatal motoneurons can be protected from axotomy-induced cell death by application of BDNF (Sendtner et al. 1992; Yan et al. 1992), and this effect was also observed in embryonic chick after limb bud removal (Oppenheim et al. 1992). These findings suggested that the TrkB-mediated response of developing motoneurons to BDNF undergoes alterations during development and might differ from the prototypic response of embryonic sympathetic or sensory neurons to NGF. This hypothesis is also supported by findings from NGF (Crowley et al. 1994; Ruberti et al. 2000) and BDNF (Liu et al. 1995) gene knockout mice. Whereas NGF knockout mice show massive developmental cell death of sympathetic or sensory neurons (Crowley et al. 1994; Ruberti et al. 2000), no enhanced loss of motoneurons could be observed in BDNF and NT-4 knockout mice (Liu et al. 1995), indicating that the dependency and response of developing sensory and motoneurons to neurotrophins differ. A difference in response of TrkA- and TrkB-expressing neurons became also apparent from experiments with stem cell–derived neurons showing that TrkB, unlike TrkA and TrkC, does not induce cell death in absence

of its ligand (Nikoletopoulou et al. 2010). This implies that BDNF responsiveness, in contrast to the response to NGF or NT-3, is a highly regulated process that depends on co-factors and modulators. This review focuses on those modulatory mechanisms in neurons that regulate responsiveness to BDNF.

Regulation of TrkB cell surface expression

First insights into the mechanisms that modulate responsiveness to BDNF in developing neurons came from analyses with cultured rat retinal ganglion cells (RGCs) and spinal motoneurons (Meyer-Franke et al. 1995; Meyer-Franke et al. 1998). These cultured neurons show only low responsiveness to BDNF despite robust TrkB expression levels. This low responsiveness was found to be due to low levels of TrkB at the cell surface when these neurons were cultured under serum-free conditions (Meyer-Franke et al. 1998). cAMP was identified in these studies as a key modulator of TrkB cell surface expression. This second messenger strongly induces responsiveness to BDNF in these neurons (Meyer-Franke et al. 1998). Previous studies had shown that cAMP also increases the responsiveness to other neurotrophins such as NGF in adrenal medullary derived neuronal cell lines (Birren et al. 1992). However, the effect of cAMP in these sympathoadrenal precursor cells was due to a transcriptional upregulation of TrkA expression and thus differed from the upregulation of cell surface translocation that had been observed for other transmembrane proteins such as ion pumps or transporters in non-neuronal cells (Barres et al. 1989; Lewis and de Moura 1984; Li et al. 1982; Murer and Biber 1996; Schwartz and Al-Awqati 1986; Wade 1986; Yao et al. 1996). In contrast, NT-3 mediated survival and TrkC activation in hippocampal neurons appeared independent of cAMP treatment (Ji et al. 2005). Experiments using *Xenopus* nerve-muscle co-cultures and rat hippocampal slice cultures showed that BDNF responsiveness is potentiated by cAMP analogs, while inhibition of cAMP signaling reduces TrkB phosphorylation, and cAMP alone cannot mimic the neurotrophin effects on synaptic potentiation (Boulanger and Poo 1999; Tartaglia et al. 2001). Depolarization by high K^+ levels or electrical stimulation has a similar effect as cAMP treatment. It activates Ca^{2+}-dependent adenylyl cyclases via Ca^{2+} influx through ion channels and NMDA receptors (Du et al. 2000; Xia et al. 1991). This also results in elevated cAMP levels and increased BDNF responsiveness (Meyer-Franke et al. 1995; Meyer-Franke et al. 1998). Two characteristic parameters indicate that this cAMP-induced BDNF responsiveness is due to a rapid TrkB surface transport from pre-existing intracellular pools rather than de novo transcription or translation of the mRNA for this receptor. First, BDNF responsiveness occurs in a relatively short time course of less than 5 min (Hanson Jr. et al.

1998). Second, inhibition of translation with cycloheximide is unable to block cAMP-mediated BDNF responsiveness (Cheng et al. 2011; Du et al. 2000; Meyer-Franke et al. 1998; Zhao et al. 2009). Furthermore, pretreatment with nocodazole or cytochalasin D prevents TrkB translocation to the cell surface, thus providing proof that cAMP-induced TrkB translocation depends on intact microtubule and actin microfilament architecture (Zhao et al. 2009).

The cAMP-mediated induction of BDNF responsiveness was observed also in other cell types such as cortical neurons (McAllister et al. 1996). cAMP itself acts in a pathway with protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K), and inhibition of either kinase drastically reduces the viability of cultured retinal ganglion cells and spinal motoneurons (Hanson Jr. et al. 1998; Meyer-Franke et al. 1995; Meyer-Franke et al. 1998). This treatment also reduces TrkB surface expression in hippocampal neurons (Cheng et al. 2011). Similarly, PI3K activity has been shown before to mediate the effects of insulin on cell surface expression of transient receptor potential cation channel (TRPV2) in Min6, CHO, and dispersed pancreatic beta-cells (Hisanaga et al. 2009). This observation revealed parallels to cAMP-induced TrkB surface translocation since it requires depolarization via Ca^{2+} entrance and an intact cytoskeleton, especially intact actin filaments (Hisanaga et al. 2009). In conclusion, cAMP was proposed to have a "gating" function that elevates translocation of TrkB via PKA and PI3K activity from intracellular stores to the cell membrane (Cheng et al. 2011; Du et al. 2000; Ji et al. 2005; Meyer-Franke et al. 1998; Zhang et al. 2000; Zhao et al. 2009).

Dynamics of TrkB cell surface translocation

TrkB cell surface translocation is accompanied by a significant enrichment of TrkB in postsynaptic spines, thus leading to a rapid enhancement in sensitivity for incoming BDNF signaling (Ji et al. 2005; Sui et al. 2015; Zhao et al. 2009). This allows BDNF-mediated short-term changes in synaptic transmission which then are further strengthened by dendritic growth and structural refinement of synapses in an activity-dependent manner (Lohof et al. 1993; Lu 2004; McAllister et al. 1999; Wang et al. 1995). In fact, BDNF stimulation increases synapse numbers in hippocampal and cerebellar neurons (Shimada et al. 1998; Tyler and Pozzo-Miller 2001) and also modulates dendritic complexity especially in the striatum (Rauskolb et al. 2010) and hippocampus (Tyler and Pozzo-Miller 2001). Association of TrkB with postsynaptic spines was further confirmed by co-localization and co-immunoprecipitation with PSD-95 which modulates guidance and anchoring of transmembrane receptors and ion channels into dendritic spines (Ji et al. 2005; Scannevin and Huganir 2000; Sheng 2001; Zhao et al. 2009). Interestingly, the

dynamics of cAMP-mediated TrkB translocation and localization in dendritic spines after chemically induced LTP (cLTP) (Zhao et al. 2009) was described to parallel AMPA receptor surface translocation under similar conditions (Yudowski et al. 2007).

BDNF secretion and local recruitment of TrkB are also crucial elements for axon differentiation (Cabelli et al. 1995). BDNF itself acts in a self-amplifying manner by promoting TrkB surface expression through elevation of cAMP and thereby drives differentiation of neurites towards axonal fate (Cheng et al. 2011; Shelly et al. 2007; Shelly et al. 2011). Thus, the differentiation of axons and dendrites seems to be controlled by redistribution of cAMP-/PKA-sensitive autocrine BDNF secretion and TrkB surface expression towards the axon (Cheng et al. 2011). Local changes in cAMP levels and PKA activity can induce axon formation in rat hippocampal neurons by modulating LKB1 and SAD kinases (Barnes et al. 2007; Kishi et al. 2005; Shelly et al. 2007). Such local cAMP changes could also fine-tune individual axonal terminals, as shown in *Drosophila* motoneurons (Maiellaro et al. 2016). This could be important for neurons with high numbers of axonal terminals, such as spinal motoneurons because it allows autonomic regulation of BDNF responsiveness at each individual axon terminal within the same neuron. Similarly, BDNF responsiveness could be regulated by TrkB surface translocation into individual dendritic spines, a process that was observed in cultured hippocampal neurons (Ji et al. 2005).

In summary, these studies provide evidence that cAMP-mediated TrkB surface translocation in dendritic spines but also axon terminals involves several critical steps (Fig. 1). First, neuronal activity triggers Ca^{2+} entry via AMPA and NMDA receptors (a). Ca^{2+} stimulates adenylyl cyclase activity, thus causing an elevation of cAMP levels which trigger PKA and PI3K activity (b). This leads to the mobilization of a rapidly available intracellular reserve pool of TrkB (c). TrkB containing vesicles are transported in a microtubule-dependent manner to distinct sites at the cell surface where they integrate, such as dendritic spines. In the dendritic target area, TrkB is transported in an actin-dependent manner via Myosin Va and associates with PSD-95 for guided integration into the PSD (d). TrkB is then able to bind BDNF and gets activated via autophosphorylation at C-terminal tyrosine residues (e).

The role of G protein–coupled receptors in TrkB signaling

Elevated levels of cAMP play a central role in the translocation of TrkB to distinct cell surface regions within neurons. Thus, it is not surprising that G protein–coupled receptors (GPCRs) were proposed as key activators and potential central
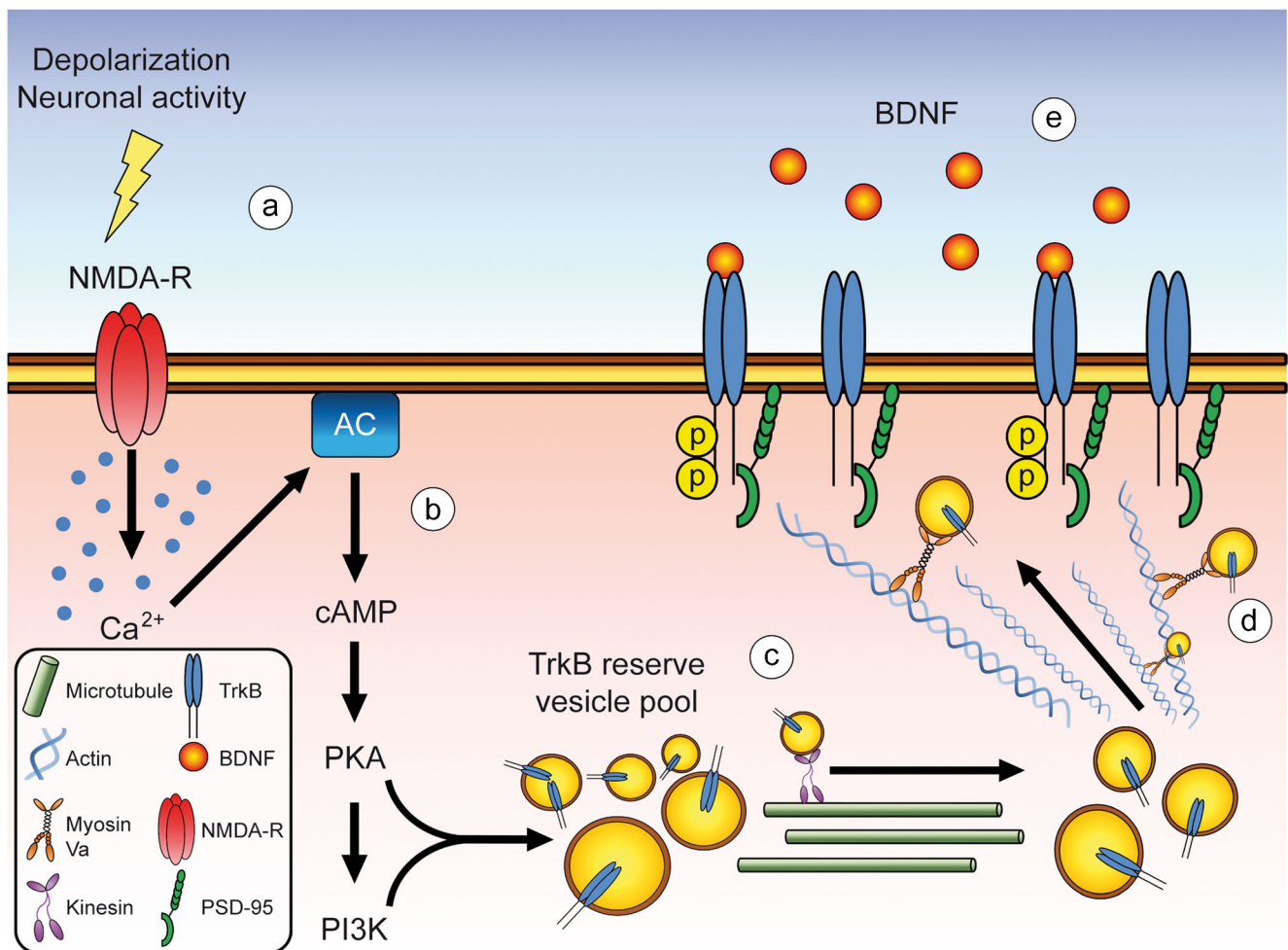
Fig. 1 Schematic representation of cAMP-mediated TrkB surface translocation via PKA/PI3K. Neuronal activity triggers Ca^{2+} entry via AMPA and NMDA receptors (a). Ca^{2+} stimulates adenylyl cyclase activity followed by elevation of cAMP levels which trigger PKA and PI3K activity (b). Rapidly available intracellular reserve pools of TrkB are mobilized in a microtubule-dependent manner (c). TrkB containing vesicles are transported to distinct target sites at the cell surface, like dendritic spines where they integrate. In the dendritic target area, TrkB is transported via Myosin Va in an actin-dependent manner and associates with PSD-95 which promotes guided transport and integration into the PSD (d). At the cell surface, TrkB is sensitive for BDNF binding which activates TrkB via phosphorylation at C-terminal tyrosine residues (e)

physiological regulators for the effects observed in cultured neurons after cAMP treatment (Ji et al. 2005; Luttrell 2008).

G protein–coupled receptors (GPCRs) constitute the largest and most diverse family of transmembrane receptors (for review see (Huang and Thathiah 2015; Luttrell 2008)). Intracellular signal transduction mediates cell proliferation, growth, differentiation, and neurotransmission including synaptic plasticity through modulation of presynaptic and postsynaptic architecture and transmitter release (Gainetdinov et al. 2004; Huang and Thathiah 2015; Luttrell 2008). Ligand binding to GPCRs causes dissociation of G_α subfamily members of G proteins which modulate the activity of effector enzymes like adenylyl cyclases (AC), phospholipase C (PLC), or L- and N-type Ca^{2+} channels (Luttrell 2008). GPCRs can change the concentration of second messenger molecules like cAMP via this G_α signaling pathway and thus modulate PKA activity (Luttrell 2008). In parallel, released

$G_{\beta\gamma}$ subunits modulate PKC activity and Ca^{2+} release from the endoplasmic reticulum (ER) via stimulation of phospholipase C-beta (PLC-β) activity (Clapham and Neer 1993; Morris and Scarlata 1997; Yan et al. 1999). Due to the ability to change cAMP and Ca^{2+} levels, GPCRs potentially modulate TrkB surface translocation. Early evidence supporting this hypothesis has been provided by studies using cultured striatal medium spiny neurons (MSNs) (Du et al. 1995). This work showed that dopamine addition potentiated the effects of BDNF on the differentiation of tyrosine hydroxylase–positive striatal neurons. This finding was supported by subsequent studies both in vivo and in vitro (Li et al. 2012; Plotkin et al. 2014). Taken together, these studies suggested that the sensitivity of striatal neurons to BDNF depends on a "co-factor". In particular, $G_{\alpha s}$–coupled GPCRs which elevate cAMP levels were found to promote corticostriatal LTP, a mechanism which most likely also involves BDNF/TrkB

signaling (Plotkin et al. 2014; Shen et al. 2008, 2016; Zhai et al. 2019). Indeed, LTP of corticostriatal synapses was found to depend on coordinated activation of NMDARs, TrkB, and $G_{\alpha s}$–coupled GPCRs like DRD1 or adenosine type 2A receptors (A_2A-R) (Plotkin et al. 2014; Shen et al. 2008, 2016; Zhai et al. 2019). However, the precise role of TrkB in this context remained undefined. Stimulation of $G_{\alpha s}$–coupled DRD1 can elevate TrkB surface expression in mixed cultures of striatal neurons (Iwakura et al. 2008) after periods of several hours. However, it remained unclear whether the increased cell surface expression was due to enhanced expression on the transcriptional and/or translational level, or enhanced cell surface translocation from pre-existing intracellular pools. It is tempting to speculate that the effects of D1 receptors on striatal LTP (Plotkin et al. 2014; Shen et al. 2008, 2016; Zhai et al. 2019) and the effects of D2 receptor stimulation on striatal LTD (Kreitzer and Malenka 2005; Shen et al. 2008, 2016; Zhai et al. 2019) involve alterations in BDNF/TrkB signaling. However, the mechanisms for this effect are still unresolved. In particular, the question remains to be determined whether alterations in transcriptional or translational control or rapid effects on subcellular transport are responsible. The relatively long time course of several hours observed for altered TrkB surface expression after D1 stimulation in cultured striatal neurons (Iwakura et al. 2008) suggests that transcriptional and translational controls are involved. However, this stands in contrast to the rapid effects of enhanced BDNF responsiveness within minutes after treatment of hippocampal neurons with agonists for dopamine or adrenergic receptors (Ji et al. 2005). If the hypothesis that GPCR signaling acts as "co-factor" to promote BDNF sensitivity via TrkB surface translocation is correct, one would also expect that ablation of this "cofactor" has similar consequences as ablation of BDNF or TrkB. Dopamine depletion is known to cause massive spine loss on striatal neurons (Day et al. 2006; Deutch 2006; Deutch et al. 2007; Gerfen 2006; Ingham et al. 1989; Ingham et al. 1998; McNeill et al. 1988; Villalba et al. 2009; Villalba and Smith 2010; Zaja-Milatovic et al. 2005) and altered LTP/LTD (Plotkin et al. 2014; Shen et al. 2008, 2016; Zhai et al. 2018). Similarly, conditional postnatal depletion of BDNF (Li et al. 2012; Rauskolb et al. 2010) or TrkB (Baydyuk et al. 2011; Li et al. 2012) also causes decreased striatal volume, dendritic atrophy, and spine loss in striatal MSNs, while scavenging of striatal BDNF suppresses corticostriatal LTP (Jia et al. 2010).

The role of N-glycosylation in cargo translocation from the ER

Apart from the ability to modulate TrkB surface translocation, GPCRs are also known to activate Trk receptors in the absence of neurotrophins, a process called transactivation (Iwakura et al. 2008; Lee and Chao 2001; Wiese et al.

2007). Similar transactivation effects were also observed in early cortical neurons when these cells were treated with epidermal growth factor (EGF) via activation of the EGF transmembrane tyrosine kinase receptor (EGFR) (Puehringer et al. 2013). TrkB plays a critical role for the migration of these early neurons (Bartkowska et al. 2007; Medina et al. 2004) at developmental stages when endogenous BDNF is still not expressed (Maisonpierre et al. 1990; Puehringer et al. 2013). This raises the question of how TrkB is activated in this developmental context. Phosphorylation of TrkB is not reduced in E12 brain of BDNF/NT-3 double knockout mice. Instead, a massive reduction of TrkB activation was observed in EGFR KO brain at this stage (Puehringer et al. 2013). In the same early cortical neurons, TrkB transactivation by EGFR signaling was also found to drive TrkB translocation from intracellular stores to the cell surface (Puehringer et al. 2013). This endogenous TrkB appeared to be recruited from the endoplasmatic reticulum to the cell surface within a few seconds (Fig. 2). Inhibition of N-glycosylation disturbed this process by abolishing retention of TrkB in the ER. This indicates that TrkB N-glycosylation plays a central role in the rapid recruitment and translocation of this receptor from the ER to the cell surface.

Glycan structures on newly synthesized glycoproteins are crucial for protein secretion. N-glycosylation is the most frequent form of posttranslational modification in the ER (Moremen et al. 2012). During this process, glycans are transferred from a lipid-linked oligosaccharide to the nascent polypeptide chain during translation (Moremen et al. 2012). After this initial transfer, trimming of two glucose residues and sequential addition of diverse monosaccharides like glucose (Glc), N-acetylgalactosamine (GalNAc), or mannose (Man) modifies the core oligosaccharide (Moremen et al. 2012). Upon proper folding, the protein normally exits the ER and traverses the Golgi apparatus. Within the Golgi apparatus, the attached glycans are further processed by trimming and extension, creating a huge diversity of potential N-glycans (Moremen et al. 2012). While the ER is present in all compartments of the neuron, including dendrites and axons, the Golgi apparatus is usually confined to the cell body (Yadav and Linstedt 2011). This raises the question of how fast translocation of TrkB from Golgi could occur in dendrites and axonal regions that are far distant from the cell body. Golgi outputs have been identified in dendrites of rat hippocampal (Hanus and Ehlers 2008; Horton and Ehlers 2003; Mikhaylova et al. 2016; Torre and Steward 1996) and spinal motoneurons (Gardiol et al. 1999), and these sites seem to be in close association with ER structures for local synthesis of transmembrane proteins, at least in dendritic microdomains. Such regions could also contain TrkB, based on its association with the ER-Golgi intermediate compartment (ERGIC) and the cis-Golgi (Schecterson et al. 2010). Nevertheless, translocation of TrkB via ERGIC and Golgi seems unlikely to be a
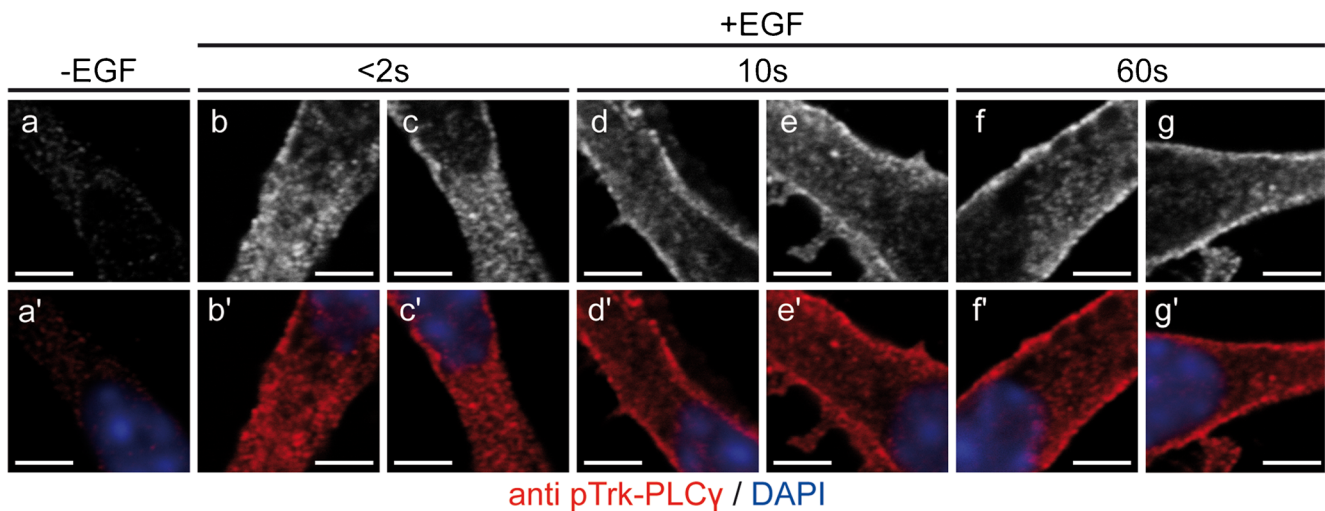
Fig. 2 Rapid TrkB surface translocation upon EGF stimulation of cortical precursor cells. Time course of pTrk-PLCγ activation after EGF stimulation in cortical precursor cells (a–g: pTrk-PLCγ-IR; a′–g′: merged images). Immediately after the EGF pulse, after less than 2s (b, b′), the signal for pTrk-PLCγ appears first intracellularly and subsequently at the cell membrane after 10s (d/d′–g/g′). Bar: 3 μm. Figure reproduced with permission from Puehringer et al. Nature Neurosci. 2013

fast process that occurs within seconds. This raises questions on the mechanisms of how TrkB could be recruited within seconds from intracellular stores to specific domains on the cell surface.

An unconventional secretory pathway from the ER to the cell surface that is independent of the Golgi apparatus has recently been described (Hanus et al. 2016). In dendrites, hundreds of "immature" core-glycosylated proteins reach the cell surface without being further modified in the Golgi. These proteins mainly function in the context of neuronal development and synaptic plasticity (Hanus et al. 2016). This suggests that dendritic and probably also axonal proteins can be directly translocated from the ER to the cell surface. Notably, TrkB has also been identified among these "immature" core-glycosylated proteins (Hanus et al. 2016). The Trk receptor family contains nine sites for potential N-glycosylation of which four are highly conserved (Watson et al. 1999). This is in line with findings that the N-glycosylation of Trk receptors contributes to cell surface translocation in early developing cortical neurons (Puehringer et al. 2013). In these cells, TrkB is densely expressed but mostly localized in the ER so that these early cortical neurons lack sufficient TrkB cell surface expression to respond to BDNF stimulation. The cell surface translocation is initiated by Src and Fyn-induced phosphorylation of C-terminal Shc and PLCγ sites of TrkB. Thus, transactivation via Src kinases appears as an important event during early postnatal development. A similar observation was made in hippocampal neurons in which TrkB phosphorylation of Ser478 in the juxtamembrane cytoplasmic region by cLTP-induced cyclin-dependent kinase 5 (Cdk5) activity leads to rapid TrkB recruitment to the cell surface (Zhao et al. 2009). The intracellular retention of TrkB within the ER

seems to be regulated by N-glycosylation (Puehringer et al. 2013). Treatment with tunicamycin that inhibits the first step of N-glycosylation causes enhanced cell surface translocation of TrkB (Puehringer et al. 2013). In contrast to acting as a retention signal for TrkB and TrkC in early cortical precursors, N-glycosylation of TrkA on at least 9 glycosylation sites has been reported as a requirement for reaching the cell surface in PC-12 cells to respond to its ligand NGF (Schecterson et al. 2010; Watson et al. 1999). Inhibition of TrkA N-glycosylation by tunicamycin in PC12 cells led to an unglycosylated TrkA core protein that remained intracellular and showed ligand-independent autophosphorylation of the Shc binding site, without being able to induce Erk1/2 downstream signaling (Watson et al. 1999). These data indicate that TrkA requires N-glycosylation for cell surface translocation (Watson et al. 1999), while TrkB does not (Puehringer et al. 2013). Similar effects of N-glycosylation were also observed for insulin receptors that are retained intracellularly within the ER upon glucose deprivation or tunicamycin treatment, both of which result in a deglycosylated receptor of reduced size (Hwang and Frost 1999; Ronnett et al. 1984). Also, the translocation of other transmembrane proteins from the ER to the cell surface, such as the ß1 subunit of the Na-K-ATPase and occludin, are regulated by mechanisms involving N-glycosylation (Vagin et al. 2009).

Taken together, N-glycosylation appears as a modulatory mechanism for retention or export of Trk receptors from the ER. While TrkA and insulin receptors require N-glycosylation for surface export, the same condition retains TrkB in the ER, leading to the conclusion that N-glycosylation has individual effects on distinct Trk receptors. Notably, TrkB export from the ER after EGF-mediated transactivation is a very fast

process and occurs within seconds. For this reason, it appears unlikely that this mechanism involves processing in the ERGIC and Golgi. This observation rather favors the idea of a direct ER export to the cell surface (Puehringer et al. 2013). However, transactivation of TrkB by GPCRs appears to follow a slower time course and seems to involve ERGIC and Golgi (Iwakura et al. 2008; Schecterson et al. 2010). More work needs to be conducted in order to understand the individual mechanisms which control Trk receptor N-glycosylation and its role for surface expression in different populations of neurons.

Conclusion

The development and function of neuronal networks, especially correct communication and adequate responses to incoming synaptic signals, crucially depend on neurotrophin signaling. TrkB and TrkA differ in the way how they induce cell death in the absence of corresponding ligands (Nikoletopoulou et al. 2010), and TrkB has additional functions beyond promoting survival and differentiation. It modulates neuronal migration and network formation during development (Bartkowska et al. 2007; Medina et al. 2004). TrkA and TrkB also differ in the way how these receptors modulate synaptic plasticity (Bibel and Barde 2000; Poo 2001). Furthermore, the activation of TrkB and responsiveness to BDNF shifts from ligand-independent transactivation during early stages of development towards BDNF-induced receptor activation at later stages.

The regulation of TrkB cell surface expression has many advantages for the function of BDNF/TrkB signaling in the context of synaptic plasticity. Changes in subcellular cAMP could act in a highly local manner and thus fine-tune individual synapses (Maiellaro et al. 2016) in dendrites and axons, without affecting others within the same neuron. This has major consequences for shaping neuronal circuits. However, such mechanisms require fast responses, and this can only be achieved when TrkB can be recruited within a very short time from intracellular stores towards synaptic sites (Ji et al. 2005; Puehringer et al. 2013). A rapid mechanism for translocating TrkB from intracellular to defined sites at the cell surface could play a central role in such circuits, by integrating responses from firing neurons that release neurotransmitters for modulating TrkB cell surface expression via corresponding GPCRs and other neurons that release BDNF. The movement of TrkB from the ER to synaptic sites in an N-glycosylation-dependent manner, by circumventing the Golgi (Hanus et al. 2016), could provide such a rapid mechanism that alters target cell responsiveness for BDNF within seconds.

So far, it remains elusive whether the simultaneous activity of different afferents is required to induce BDNF-/TrkB-mediated LTP in such circuits. LTP then would be induced in a spatio-temporal manner only when both afferents are active. On the other side, such a scenario also would require a highly precise mechanism for removal of TrkB from the cell surface, and it is not clear whether this occurs only after ligand-induced endocytosis or also by other mechanisms. Alterations of such control mechanisms could cause aberrant synaptic plasticity and network communication and thus might be involved in numerous neuropsychiatric diseases.

Compliance with ethical standards

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