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The dual role of BDNF in epilepsy: insights from calpain-mediated TrkB-FL cleavage

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ABSTRACT

Despite the efficacy of current antiseizure medications in managing seizures, approximately one-third of patients develop refractory epilepsy, highlighting an urgent need to uncover the molecular mechanisms driving epileptogenesis. This process emerges from a complex interplay of molecular alterations, involving changes in neuronal signaling pathways. Among these, brain-derived neurotrophic factor (BDNF) and its high-affinity receptor, the full-length tropomyosin receptor kinase B (TrkB-FL), are heavily implicated in epilepsy pathophysiology. While traditionally recognized for promoting synaptic plasticity, BDNF signaling can become maladaptive in pathological states. Consequently, BDNF exhibits a paradoxical dual role in epilepsy, acting as a pro-epileptogenic factor in the acute phase, while exerting antiepileptic effects during the chronic phase. Recently, a calpain-dependent proteolytic mechanism mediating TrkB-FL cleavage, previously described in Alzheimer's disease (AD) and cerebral ischemia, has been shown to occur during epileptogenesis. Elevated levels of the intracellular cleavage product of TrkB-FL, TrkB-ICD, have been observed in the hippocampus of patients with refractory epilepsy, establishing its clinical relevance. In vitro, TrkB-ICD overexpression depolarizes neuronal membranes, increases miniature excitatory postsynaptic current frequency, and alters the transcription of genes related to synaptic transmission and plasticity. In vivo, its overexpression induces long-term memory impairment, a common comorbidity in epilepsy. Moreover, in experimental epilepsy models, TrkB-ICD protein levels correlate with seizure frequency during the acute phase (*status epilepticus*) and remain elevated during the chronic phase (established epilepsy). These findings highlight TrkB-FL cleavage and TrkB-ICD formation as molecular determinants in epileptogenesis, providing a biological rationale for the contrasting effects of BDNF. Inhibiting this cleavage, using tools like cell-penetrating peptides, represents a promising therapeutic avenue. As the field moves forward, elucidating the precise functions, regulation, and translational potential of TrkB-FL proteolysis and TrkB-ICD formation may yield innovative, disease-modifying strategies for epilepsy, moving beyond the symptomatic suppression offered by conventional antiseizure drugs.

Abbreviations: Akt, protein kinase B; BDNF, brain-derived neurotrophic factor; CA1, cornu ammonis 1; CA3, cornu ammonis 3; CREB, cAMP response element binding protein; DG, dentate gyrus; i.c.v., intracerebroventricular; i.p., intraperitoneal; KA, kainic acid; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated protein kinase; NGF, nerve growth factor; NPY, neuropeptide Y; $p75^{NTR}$, pan-neurotrophin receptor; PI3K, phosphatidylinositol-3′-kinase; PKC, protein kinase C; PLCγ, phospholipase C γ; Pro-BDNF, pro-brain-derived neurotrophic factor; s.c., subcutaneous; SE, status epilepticus; SRCS, spontaneous recurrent convulsive seizures; TAT, transactivator of transcription; TLE, temporal lobe epilepsy; TrkB-FL, full-length tropomyosin receptor kinase B; TrkB-ICD, calpain-mediated intracellular fragment from tropomyosin receptor kinase B; TrkB-Shc, tropomyosin receptor kinase B containing the Src homology and collagen-like (Shc) domain; TrkB-T1, C-terminal 1 truncated tropomyosin receptor kinase B; TrkB-T2, C-terminal 2 truncated tropomyosin receptor kinase B; TrkB-Tc, C-terminal truncated tropomyosin receptor kinase B; TrkB-T′, calpain-mediated truncated tropomyosin receptor kinase B.

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1. Introduction

Epilepsy is a complex neurological disorder in which approximately one-third of patients develop drug resistance. Because current antiseizure medications primarily offer symptomatic relief without halting disease progression, there is a critical need to identify novel disease-modifying targets. Brain-derived neurotrophic factor (BDNF) and its high-affinity receptor, the full-length tropomyosin receptor kinase B (TrkB-FL), are implicated in epileptogenesis due to their central role in neuronal excitability and circuit remodeling. However, BDNF signaling in epilepsy presents a paradox, acting as both a proepileptogenic and antiepileptic factor depending on the disease stage. This review summarizes the current knowledge on BDNF and TrkB-FL in epilepsy, focusing on a recently identified post-translational mechanism, the calpain-mediated TrkB-FL cleavage, as a key determinant of this dual role and a promising therapeutic avenue. Furthermore, to provide a structured overview of the existing literature, relevant data on the temporal dynamics and functional impacts of BDNF/TrkB alterations were consolidated into reference tables.

2. BDNF and TrkB

2.1. BDNF location

In 1982, Yves-Alain Barde and colleagues isolated brain-derived neurotrophic factor (BDNF) for the first time from porcine brain tissue [1]. Since then, BDNF has become the most extensively studied neurotrophin, with 38,678 entries on PubMed, compared to 18,675 for nerve growth factor (NGF), the first neurotrophin discovered (accessed on 28.06.2026). This extensive literature reflects the central role of BDNF in synaptic plasticity, neuronal excitability, and circuit remodeling, processes that are critically involved in the pathophysiology of epilepsy [2].

BDNF is predominantly expressed in the brain, although it is also expressed in peripheral tissues, including the heart, lung, retina, placenta, prostate, skin, thyroid, and urinary bladder [3]. Within the central nervous system, both BDNF mRNA and protein levels increase during brain development [4]. In the adult brain, the hippocampus and cerebral cortex (regions critically involved in seizure generation and propagation) exhibit the highest levels of BDNF mRNA and protein [4,5]. At the cellular level, BDNF is primarily located in neurons, particularly in glutamatergic neurons [4], aligning with its established role in modulating excitatory synaptic transmission. Lower levels of BDNF have been reported in glial cells, including astrocytes [6,7], oligodendrocytes [8–10], and activated microglia [11,12]. This broader cellular distribution suggests that BDNF may contribute not only to neuronal plasticity but also to neuroinflammatory and glial mechanisms, which are increasingly recognized as modulators of epileptogenesis. Subcellularly, BDNF is found both in presynaptic vesicles and in postsynaptic compartments of neurons [13].

The diversity of BDNF cellular and subcellular localization is closely linked to the existence of multiple BDNF transcripts with distinct regulatory and functional properties [14]. In rodents, the *Bdnf* gene comprises nine 5' non-coding exons (*I-IXa*), each associated with a specific promoter to initiate transcription, and one 3' coding exon (*IX*) [14,15]. In humans, the *BDNF* gene contains ten 5' non-coding exons (I-VIII, including Vh and VIIIh) and one 3′ coding exon (*IX*) [15,16]. Despite this transcriptional complexity, all BDNF transcripts share the same 3' coding exon and give rise to the same pre-pro-BDNF protein [15].

Pre-pro-BDNF is synthesized in the endoplasmic reticulum, where it is proteolytically cleaved into an immature protein precursor (pro-BDNF) [17,18]. Pro-BDNF is subsequently transported to the Golgi apparatus, where it is proteolytically cleaved by furin or convertases to generate mature BDNF [17,18]. Alternatively, pro-BDNF can be secreted as such and may subsequently be processed extracellularly into mature BDNF by tissue plasminogen activator/plasmin or metalloproteinases [17,18].

Pro-BDNF can also be secreted without undergoing further proteolytic cleavage, acting as a biologically active ligand, binding with high affinity to the pan-neurotrophin receptor ($p75^{NTR}$) and with lower affinity to full-length tropomyosin receptor kinase B (TrkB-FL) [17,18].

2.2. TrkB receptor isoforms and location

The TrkB gene (*Ntrk2*), which encodes the primary high-affinity receptor for mature BDNF, undergoes alternative splicing, producing multiple isoforms. In humans, the available data suggest that these splice variants can encode at least 36 distinct proteins, differing in their extracellular and/or intracellular domains [19,20]. Isoforms lacking leucine-rich motifs in the extracellular region are unable to bind BDNF, whereas those with alterations in the intracellular region lack the tyrosine kinase domain required for canonical neurotrophic signaling [19]. Among these, the full-length receptor (TrkB-FL) isoform and the truncated isoforms (TrkB-T1, TrkB-T2, and TrkB-Shc) are the most functionally relevant, with TrkB-FL mediating the canonical neurotrophic effects of mature BDNF.

TrkB-FL is predominantly expressed in the brain, although it is also detected at lower levels in peripheral tissues, including the thyroid, adipose tissue, gallbladder, and eyes [3,21]. Within the central nervous system, TrkB-FL expression increases during brain development and declines with age [22]. This developmental upregulation contrasts with the expression of the low-affinity $p75^{NTR}$, which decreases over the same period [4]. High levels of TrkB-FL expression are observed in the hippocampus and cerebral cortex [20], which are regions highly implicated in epilepsy [23]. At the subcellular level, TrkB-FL is largely produced in neurons, where it is distributed across dendrites and cell bodies and is mainly associated with the plasma membrane [24]. Although TrkB-FL expression has also been reported in astrocytes [25] and oligodendrocyte precursor cells [10], these findings are contradictory across studies and require further investigation.

Truncated isoforms lacking the catalytic kinase domain include TrkB-T1, TrkB-T2, and TrkB-Shc (depending on species), which are generated by alternative splicing, as well as a calpain-cleaved truncated isoform, which is mainly observed under excitotoxic conditions [20,21,26].

TrkB-T1 is the most abundantly expressed TrkB isoform in the brain, often exceeding TrkB-FL levels [4,21] and it is also expressed in the heart [21]. In the central nervous system, it is mainly expressed by astrocytes and, to a lesser extent, by neurons and microglia upon an insult [7,27–29]. TrkB-T2, which contains a distinct intracellular tail, has been described exclusively in the rodent brain [21,26]. In contrast, TrkB-Shc, which retains the Src homologous and collagen-like (Shc) adaptor protein binding site, appears to be selectively expressed in the human brain [19] and is nearly undetectable in rodents [4]. This species-specific expression pattern is particularly relevant when translating findings from experimental epilepsy models to human disease.

2.3. BDNF and TrkB-FL signaling

Upon secretion into the synaptic cleft, BDNF dimers bind with high affinity to the extracellular region of TrkB-FL through its third leucine-rich motif or second cysteine cluster domain [30,31]. Ligand binding induces TrkB-FL dimerization [32] and promotes receptor internalization into endosomes [33,34] (Fig. 1). Within endosomes, with its extracellular domain facing the outside of the endosome (the cytosol) [35], TrkB-FL dimers autophosphorylate on specific intracellular tyrosine residues: Tyr^{515} and Tyr^{816} [32] (Fig. 1).

Phosphorylation of Tyr^{515} enables the recruitment of the Shc adaptor protein, leading to activation of the phosphatidylinositol-3′-kinase (PI3K) and Ras pathways. PI3K activates the protein kinase B (Akt) cascade, which promotes neural proliferation [36], neuronal survival [37], and neurogenesis [38,39], thereby enhancing the processes of

learning and memory [40]. Additionally, this cascade prevents oxidative stress, inflammation, and apoptosis [39,41]. In parallel, Ras activates the mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK) cascade, promoting neuronal survival [42], cell proliferation [43], oligodendrocyte differentiation [44], and axonal outgrowth, while regulating neuronal plasticity [45,46]. In addition, some reports also show that this cascade prevents excitotoxicity [45,47] and autophagy [42].

Phosphorylation of Tyr^{816} creates a docking site for phospholipase C γ (PLCγ), triggering intracellular calcium release and the activation of protein kinase C (PKC). This signaling cascade promotes synaptic plasticity [48,49] and neuronal survival [50], and potentiates or inhibits postsynaptic $GABA_A$ responses in an age-dependent manner [51], directly linking TrkB signaling to the excitation-inhibition balance.

Interestingly, TrkB-FL can also be phosphorylated in the absence of BDNF, a process termed transactivation. Various neurotransmitters and neuromodulators, such as adenosine [52], oxytocin [53], epidermal growth factor [54], and dopamine [55], have been shown to transactivate TrkB-FL via their respective receptors (A_{2A} receptor, oxytocin receptor (OTXR), EGF receptor, and D1 receptor, respectively). In addition, the action of BDNF through TrkB-FL can also be facilitated by the activation of adenosine A_{2A} receptors [52,56–58].

Even in the presence of BDNF, TrkB-FL phosphorylation may be disrupted by an imbalance between TrkB-FL and TrkB-T1. Upregulation of truncated receptors, particularly TrkB-T1, inhibits BDNF/TrkB-FL signaling by forming non-functional heterodimers with TrkB-FL, thus acting as a dominant-negative modulator [59]. This imbalance promotes neuronal death through an excitotoxic process [27].

Therefore, both TrkB-FL/TrkB-T1 imbalance and alterations in BDNF or TrkB-FL levels may lead to impaired BDNF/TrkB-FL signaling. Such impairment has been described in several pathological conditions, including Alzheimer's disease (AD), amyotrophic lateral sclerosis, Rett syndrome, depression, Parkinson's disease, Huntington's disease, multiple sclerosis, cerebral ischemic stroke, and epilepsy [18,60–63]. Targeting this signaling pathway may represent a potential therapeutic strategy for these disorders.

2.4. BDNF and TrkB levels in epilepsy

Alterations in BDNF and TrkB-FL expression have been consistently reported in epilepsy, particularly in temporal lobe epilepsy (TLE). Increased BDNF mRNA [64] and protein levels [65] have been detected in the hippocampus of patients with intractable TLE compared with non-epileptic *post-mortem* controls. At a transcriptional level, this BDNF alteration occurs mainly in the dentate gyrus (DG) and cornu ammonis 3 (CA3) of the hippocampus [66]. In addition, a differential increase in the expression of specific BDNF transcripts has been reported in the hippocampus [67,68] and cortex [69] of drug-resistant TLE patients. Peripheral alterations have also been reported, with increased BDNF mRNA levels detected in the blood of patients with generalized tonic-clonic seizures compared to healthy subjects [70]. However, blood serum from patients with intractable TLE showed reduced levels of BDNF protein, which correlated with epilepsy duration and cognitive impairment [71], highlighting the complexity of peripheral BDNF measurements. Notably, interpreting these BDNF levels in clinical samples requires caution, as antiseizure medications may modulate BDNF expression. For example, ex vivo exposure to valproic acid for 3 h significantly reduced BDNF protein levels in hippocampal slices from patients with intractable TLE [66], whereas topiramate monotherapy was associated with the downregulation of specific BDNF transcripts in the hippocampus of patients with refractory epilepsy [68].

Evidence regarding TrkB-FL expression in epilepsy remains more limited and inconsistent. Increased TrkB-FL protein levels were reported in the DG and CA3 of patients with pharmacoresistant TLE, compared

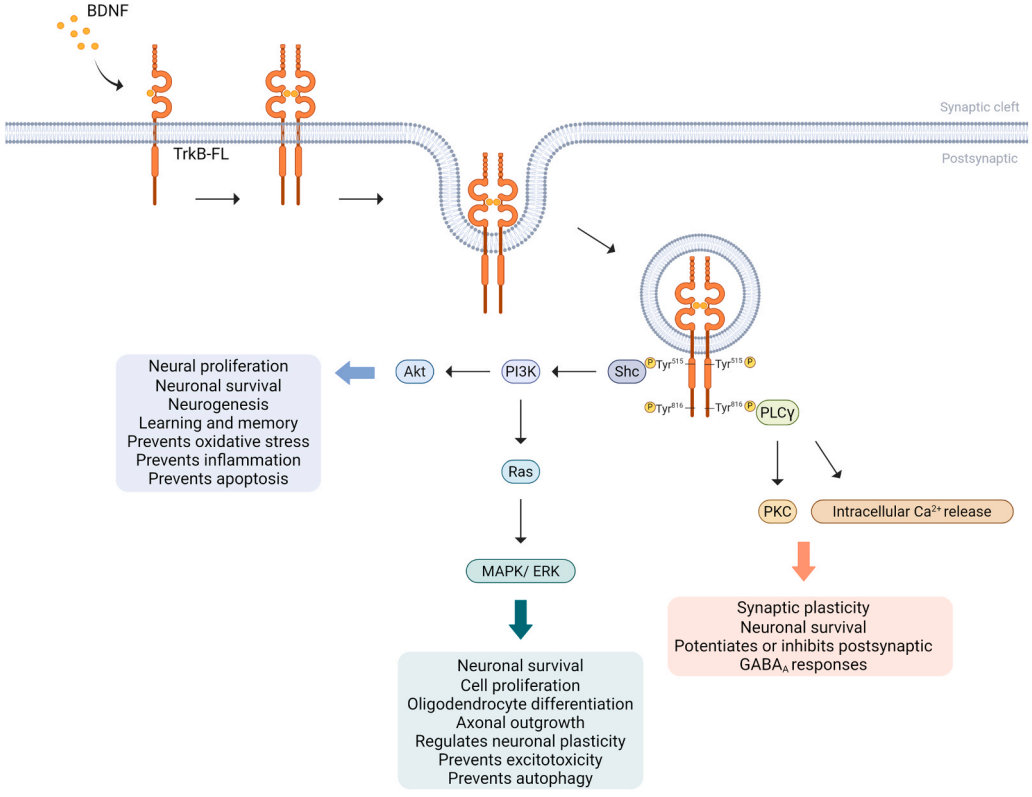

Fig. 1. BDNF/TrkB-FL signaling pathways. BDNF, brain-derived neurotrophic factor. TrkB-FL, full-length tropomyosin receptor kinase B. Shc, Src homology and collagen-like. PI3K, phosphatidylinositol-3′-kinase. Akt, protein kinase B. MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated protein kinase. PLCγ, phospholipase C γ. PKC, protein kinase C. Ca^{2+}, calcium.

with autopsy-derived hippocampal tissue from individuals without epilepsy [66]. Notably, this study excluded patients with bilateral hippocampal sclerosis or hippocampal sclerosis accompanied by other epileptogenic lesions [66]. In contrast, a more recent study found reduced TrkB-FL protein levels in whole hippocampal samples from patients with pharmacoresistant TLE when compared with hippocampal samples collected from autopsies of individuals without epilepsy [72]. Beyond the hippocampus, increased TrkB-FL protein levels have been detected in postsynaptic density protein complexes isolated from neocortical tissue of epilepsy surgery patients [73]. Moreover, allelic variants of the *NTRK2* gene have been associated with epilepsy susceptibility in humans [74]. TrkB-FL expression may also be influenced by antiseizure medication, as valproic acid exposure reduced TrkB-FL protein levels in hippocampal samples from pharmacoresistant TLE patients [66].

Findings from experimental epilepsy models largely recapitulate human data regarding BDNF upregulation, with increased BDNF mRNA and protein levels reported across multiple in vivo models of epilepsy, typically peaking at 24 h after the epileptogenic insult (Table 1). In contrast, TrkB-FL levels show marked temporal and model-dependent variability (Table 1). TrkB-FL mRNA levels have been reported to remain stable for hours or days after kainic acid (KA) administration [75,76] or to increase during this timeframe after KA, pilocarpine, or kindling [77–79]. In contrast to mRNA levels, TrkB-FL protein levels were reduced within hours and remained decreased for up to 7 days after administration of KA [80,81] or pilocarpine [82]. Consistently, TrkB-FL protein levels were also decreased minutes or hours after the insult (KA or Mg^{2+}-free medium) in in vitro models of status epilepticus (SE) [83–85]. Nevertheless, during the chronic phase of epilepsy (i.e., established epilepsy), TrkB-FL protein levels appear to diverge from these acute responses. For instance, in pilocarpine-induced epilepsy, TrkB-FL protein levels were found to be increased during established epilepsy [86].

Levels of TrkB-FL phosphorylated at the Tyr^{817} and Tyr^{515} residues were found to be decreased at 3 h, 27 h, and 7 days after pilocarpine [82] or KA [81]. In contrast, TrkB-FL phosphorylated at the Tyr^{490} residue was described to be increased 24 and 48 h after KA, and only 24 h after kindling [87]. In an in vitro model, TrkB phosphorylated at the Tyr^{817} residue was also described to be increased 3 h after SE induction [85]. Regarding the levels of truncated isoforms, the literature is congruent, showing an increased level of truncated TrkB mRNA or protein after KA, pilocarpine, or kindling [75–80,85,86].

In summary, BDNF mRNA and protein levels are robustly reported to be increased across most studies, both in human epilepsy and in experimental models. Truncated TrkB levels are increased in experimental models, although corresponding data from human tissue remain limited. In contrast, TrkB-FL expression and activation display pronounced temporal and model-dependent variability. These discrepancies likely reflect differences in seizure severity, insult type, disease stage, and sampling strategies.

2.5. Dual role of BDNF and TrkB in epilepsy

BDNF signaling through TrkB-FL exerts a dual role in epilepsy, acting as both a proepileptic and antiepileptic agent. The previously described seizure-induced upregulation of BDNF mRNA leads to increased BDNF protein production by dentate granule cells, as well as enhanced anterograde transport and release of BDNF from mossy fiber axons [89–92]. This process promotes TrkB-FL activation in the hilus and CA3 *stratum lucidum* and may contribute to mossy fiber sprouting [90]. Additionally, TrkB-FL activation has been shown to increase neuronal excitability while decreasing inhibitory synaptic transmission [90,93–95].

Multiple lines of evidence suggest that modulating either BDNF or TrkB levels before or immediately after SE is sufficient to affect SE severity or the development of spontaneous recurrent seizure (SRS)

Table 1
Temporal dynamics of BDNF, TrkB-FL, pTrkB, and truncated TrkB levels in experimental models of seizures and epilepsy.

Model	Stimulus	Timepoint assessed	Conclusions *	Ref.
		In vivo		
Periadolescent female Sprague-Dawley rats	KA (i.p.)	3 h, 6 h, 12 h, 18 h after KA	↑ BDNF mRNA (6 h) and protein = TrkB-FL mRNA (6 h) ↑ TrkB-Tc mRNA (6 h)	[75]
Adult male Sprague-Dawley rats	KA (i.p.), diazepam	3 h, 6 h, 12 h, 1d, 3d, and 7 days after KA	↑ BDNF mRNA and protein (peak at 24 h) = TrkB-FL mRNA and protein (during 7 days) ↑ TrkB-Tc (12 h)	[76]
Periadolescent male Sprague-Dawley rats	KA (s.c.)	1 h, 4 h, 4d, and 7d after KA	↑ BDNF mRNA ↑ TrkB-FL mRNA ↑ TrkB-Tc mRNA	[78]
Adult Sprague-Dawley rats	KA (i.p.), pentobarbital (i.p.) or kindling (induced only stage 1 and stage 2)	3 h, 12 h, 24 h, 48 h and 1 week after pentobarbital or 3 h, 12 h, 24 h, and 1 week after kindling	↑ pTrkB (Tyr^{490}) (at 24 h and 48 h after KA, or 24 h after kindling)	[87]
Adult male Wistar rats	KA (i.c.v.), DMSO	7 days after KA	↓BDNF ↓TrkB-FL ↓ pTrkB (Tyr^{515})	[81]
Adult male mice C57BL/6	KA (Intrahippocampal)	12 h after KA	↓TrkB-FL ↑ TrkB-Tc	[80]
Adult male mice C57BL/6J	KA (Intrahippocampal)	1, 2, 8, 14, 16, 21, and 31 days after KA	↑ BDNF mRNA and protein	[88]
Adult Male Wistar rats	Scopolamine methyl nitrate (s.c.), pilocarpine hydrochloride (i.p.), diazepam	More than 60 days after pilocarpine	↓ BDNF ↑ TrkB-FL ↑ TrkB-Tc	[86]
Adult male Wistar rats	Scopolamine methyl-bromide (i.p), pilocarpine hydrochloride (i.p.), diazepam	0 h, 12 h, 24 h, and 72 h after 3 h of SE	↑ BDNF (0 h, 24 h, 72 h; peak at 24 h) ↓ TrkB-FL (12 h, 24 h, 72 h) ↓ pTrkB (Tyr^{817}) (0 h, 24 h) = TrkB-Tc	[82]
Adult male Sprague-Dawley rats	N-methyl-scopolamine (s.c.), pilocarpine (i.p.)	1 h, 3 h, 6 h, and 24 h after pilocarpine	↑ BDNF mRNA (1 h, 3 h, 6 h, 24 h) ↑ TrkB mRNA (3 h, 6 h)	[79]
Adult Sprague Dawley rats	Kindling	1 h, 2 h, 3 h, 6 h, 12 h, 24 h, 26 h and 96 h after the stimulus	↑ BDNF mRNA	[89]

(*continued on next page*)

Table 1 (*continued*)

Model	Stimulus	Timepoint assessed	Conclusions *	Ref.
Adult male Sprague-Dawley rats	Electroconvulsive seizures for 10 days	2 h and 18 h, after the last electrical stimulation	↑ BDNF mRNA (2 h, 18 h) ↑ TrkB mRNA (2 h, 18 h)	[77]
		In vitro		
Primary rat hippocampal neuronal culture	Mg^{2+} free	1 h, 2 h, 3 h, and 24 h after SE induction	↓ TrkB-FL mRNA and protein ↑ TrkB-Tc mRNA and protein	[83]
Primary rat hippocampal neuronal cultures	Mg^{2+} free	3 h and 9 h after SE induction	↓ TrkB-FL ↑ pTrkB (Tyr^{817}, at 3 h) ↑ TrkB-Tc	[85]
Primary rat hippocampal neuronal cultures	KA	30, 60, and 90 min after KA	= BDNF ↓ TrkB-FL (30, 60 or 90 min)	[84]

Abbreviations: KA, kainic acid. BDNF, brain-derived neurotrophic factor. TrkB-FL, full-length tropomyosin receptor kinase B. TrkB-Tc, C-terminal truncated tropomyosin receptor kinase B. i.p., intraperitoneal. s.c., subcutaneous.

* Except if stated otherwise, data correspond to variations in protein levels.

(Table 2). Collectively, an increase in BDNF or TrkB-FL levels promotes hyperexcitability and susceptibility to epileptic insults and increases seizure severity [88,96–98]. Contrastingly, a decrease in the levels of these proteins has the opposite effect, reducing susceptibility to epileptic insults, delaying seizure onset, and decreasing or even suppressing spontaneous seizure development [99–103]. Furthermore, reducing TrkB-FL phosphorylation through TrkB-T1 overexpression has also been shown to impair epileptogenesis [88,104].

Moreover, BDNF/TrkB signaling pathway-related proteins can also have an impact on epileptogenesis. Transgenic mice with decreased levels of the cAMP response element binding protein (CREB), a transcription factor activated by all three pathways triggered by BDNF/TrkB binding, developed fewer SRS after pilocarpine-induced SE or displayed a delayed seizure progression during kindling [105]. Similarly, the inhibition of mammalian target of rapamycin (mTOR), a protein kinase activated by the PI3K/Akt and MAPK/Erk pathways, decreased SRS frequency after electrical stimulation [106] or pilocarpine administration [107]. Nevertheless, the genetic disruption of TrkB-Shc signaling failed to affect SE severity and instead exacerbated hippocampal neuronal death induced by SE [108]. Remarkably, the transient inhibition of TrkB-PLCγ1 signaling following an evoked seizure reduced the duration and severity of spontaneous recurrent convulsive seizures (SRCS) during the subsequent 14 days [109] or decreased SRCS frequency for 42 days after KA injection [110].

In contrast to its acute proepileptic effects, chronic hippocampal BDNF delivery exerts antiseizure actions [90,94,95]. Chronic administration of BDNF in the hippocampus has been shown to promote the suppression of seizure development [111–113]. Particularly, the continuous hippocampal secretion of BDNF over 3 weeks during SRCS resulted in a reduction in seizure frequency in a pilocarpine model of epilepsy [114]. A similar study demonstrated that chronic infusion of BDNF decreased the levels of TrkB-FL and pTrkB at the Tyr^{490} residue, while also inhibiting the development of SRCS [97].

TrkB-FL internalization has also been proposed as a putative mechanism by which chronic BDNF infusion decreases seizures [90,94,95]. This hypothesis suggests that BDNF signaling may be reduced due to TrkB-FL internalization. However, this interpretation is debatable, since the internalization of TrkB-FL occurs after BDNF binding and is a critical step to initiate signal transduction and activation of signaling pathways

Table 2
Impact of BDNF and TrkB-FL gain- or loss-of-function on seizure susceptibility and epileptogenesis.

Approach	Model		Conclusions	Reference
		BDNF		
BDNF (+/-) heterozygous mice	Kindling mouse model	(↓)	Delay in exhibiting generalized convulsive seizures	[99]
BDNF conditionally deleted	Kindling mouse model	(↓)	Delay in exhibiting generalized convulsive seizures	[101]
BDNF-overexpressing transgenic mice	KA i.p. mouse model	(↑)	Increased number of severe seizures	[96]
BDNF overexpression in astrocytes	KA i.p. combined with the kindling mouse model	(↑)	Higher excitability of hippocampal CA3 –CA1 synapses Longer seizure duration	[98]
BDNF microinjected 3 times in the hippocampus	Kindling rat model	(↑)	BDNF alone induced electrographic seizures Higher susceptibility to kindling and increased behavioral seizure severity	[97]
		TrkB-FL		
TrkB-FL conditionally deleted	Kindling mouse model	(↓)	Inhibition of convulsive seizure development	[101]
TrkB-FL-overexpressing transgenic mice	KA intra-hippocampal mouse model	(↑)	Less time to spontaneous recurrent electrographic seizure onset Higher spontaneous recurrent electrographic seizure severity	[88]
Chronic i.c.v administration of TrkB–Fc (BDNF scavenger)	Kindling rat model	(↓ TrkB-FL)	Delayed kindling development Inhibition of generalized convulsive seizure development	[100]
TrkB-FL protein expression *de novo* reduction	Kindling mouse model	(↓)	Delay in exhibiting generalized convulsive seizures. In some cases, inhibition of generalized convulsive seizure development	[102]
TrkB-FL activation inhibition after SE	KA intra-amygdala	(↓)	Prevention of spontaneous recurrent seizure development	[103]
Truncated TrkB				
TrkB-T1-overexpressing transgenic mice	KA i.p. mouse model	(↑)	Lower frequency of interictal spiking Delay in spontaneous recurrent seizure onset Less frequent and severe spontaneous recurrent seizures	[104]
TrkB-T1-overexpressing transgenic mice	KA intra-hippocampal mouse model	(↑)	Delay in spontaneous recurrent electrographic	[88]

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Table 2 (*continued*)

Approach	Model	Conclusions	Reference
		seizure onset Reduced severity of spontaneous recurrent electrographic seizure	

Abbreviations: KA, kainic acid. BDNF, brain-derived neurotrophic factor. TrkB-FL, full-length tropomyosin receptor kinase B. TrkB-T1, C-terminal 1 truncated tropomyosin receptor kinase B. i.p., intraperitoneal. CA1, cornu ammonis 1. CA3, cornu ammonis 3. i.c.v., intracerebroventricular.

[33,34] rather than a process that simply prevents ligand binding. Additionally, the internalization of TrkB-FL may represent a protective mechanism against its cleavage by calpains. As will be discussed in greater detail later in this review, calpain-mediated cleavage of TrkB-FL generates the fragment TrkB-ICD, which has been associated with pro-epileptic effects.

Another mechanism that could explain the antiseizure effect of chronic BDNF infusion is the production of neuropeptide Y (NPY). NPY protein levels were upregulated 7 days after chronic BDNF infusion in the hippocampus [115]. NPY itself can also delay the development of spontaneous seizures, while antibodies against this neuropeptide reverse these effects [116]. Transgenic mice lacking NPY experienced prolonged seizures and exhibited a higher mortality rate during KA-induced SE. However, this mortality was effectively prevented by the intracerebroventricular infusion of NPY before the KA injection [117].

2.6. TrkB-FL cleavage in epilepsy and other conditions

The mechanism underlying the decrease in TrkB-FL protein levels mediated by calpains began to be unraveled around a decade ago. In 2012, it was demonstrated that TrkB-FL protein levels decreased while truncated isoforms (~95 kDa) increased in cultured neurons treated with glutamate or NMDA [27,80]. Moreover, in vivo unilateral injection of KA into the mouse hippocampus also produced similar results [80]. Simultaneously, calpain inhibition prevented TrkB-FL levels from decreasing under excitotoxic conditions (glutamate, NMDA) [27,80]. At this point, it was thought that the upregulation of TrkB truncated isoforms should occur through a transcription-dependent mechanism [27,80]. However, Vidaurre and colleagues demonstrated that these TrkB truncated isoforms (~95 kDa) comprised not only TrkB-T1 but also a novel product of calpain-dependent TrkB-FL processing [27].

Indeed, in cultured neurons exposed to amyloid-β, calpains cleaved TrkB-FL, generating a new membrane-bound truncated receptor (TrkB-T') and an intracellular fragment (TrkB-ICD) [26]. Likewise, in cultured neurons submitted to a SE-like insult (Mg^{2+}-free medium), a calpain-dependent decrease in TrkB-FL protein levels and an increase in truncated isoforms were demonstrated, although TrkB-ICD was not evaluated [85]. Calpain activation has also been previously observed in an in vivo model of SE using KA (10 mg/kg, i.p.) [118].

Altogether, it was demonstrated that excitotoxicity promotes TrkB dysregulation through: 1) increasing the transcription of the truncated TrkB-T1 isoform, and 2) the calpain-dependent cleavage of TrkB-FL, generating a novel truncated form, TrkB-T', and an intracellular domain, TrkB-ICD. TrkB-FL cleavage has been studied in several disease contexts, both in vitro and in vivo, and in human samples (Table 3). However, less is known about the resulting fragments and their impact on cellular and tissue physiology. TrkB-T' may function as a negative modulator of BDNF/TrkB-FL signaling, promoting cell death [85], whereas TrkB-ICD may interfere with TrkB-FL transcriptional regulation [119]. TrkB-ICD has an estimated half-life of 8 h and can be detected in both the nucleus and cytosol of neurons [119]. In TrkB-ICD-transfected primary neurons, the fragment accumulated in the nucleus 16–24 h after transfection and phosphorylated neuronal proteins via its tyrosine kinase activity [119]. Additionally, TrkB-ICD overexpression in cultured neurons was shown to induce dendritic spine loss, neuronal depolarization, increased frequency of miniature excitatory postsynaptic currents (mEPSCs), and alterations in the expression of genes involved in synaptic transmission and plasticity [120]. Notably, one of the genes regulated by TrkB-ICD was *Npy2r* [120], which encodes the neuropeptide Y2 receptor. Increased NPY2r mRNA levels have been consistently reported during SE and established epilepsy in rodent models and patients [121–124]. As the Y2 receptor is known to inhibit glutamate release [121], the TrkB-ICD-induced upregulation of this receptor may represent a compensatory neuroprotective mechanism that counteracts the deleterious effects of TrkB-ICD signaling. Moreover, TrkB-ICD overexpression in the hippocampi of healthy rodents induced long-term memory impairment in behavioral tasks, accompanied by an exaggerated and potentially dysfunctional enhancement of long-term potentiation (LTP) [72]. In the human brain, TrkB-ICD protein levels were elevated in hippocampal tissue resected from patients with refractory epilepsy [72] and in postmortem samples of the inferior temporal cortex from patients with Alzheimer's disease [120].

Other products of excitotoxicity-mediated TrkB cleavage have been described in cultured cortical neurons exposed to NMDA [24]. In addition to the 32 kDa fragment, which resembles the TrkB-ICD described in [26], minor amounts of 42 and 39 kDa fragments were also detected. The 42 kDa fragment is a product of TrkB-FL cleavage by metalloproteinases, rather than calpains, and it is subsequently processed by

Table 3
Calpain-dependent TrkB-FL cleavage and TrkB-ICD formation in models of different disorders/ conditions.

Disease/ Condition	Finding	*In vitro*	*In vivo*	Humans Samples
AD	TrkB-FL ↓, TrkB-T' or Tc ↑	[26, 125]	[120]	[120]
	TrkB-ICD formation	[26]	[120]	[120]
	Calpains activation	[26]	[126]	[127]
Epilepsy	TrkB-FL ↓, TrkB-T' or Tc ↑	[85]	[80]; only TrkB-FL [72]	only TrkB-FL [72]
	TrkB-ICD formation	-	[72]	[72]
	Calpain activation	[83, 85]	[118]	-
Glutamate/ NMDA	TrkB-FL ↓, TrkB-T' or Tc ↑	[27, 80, 128]	-	-
	TrkB-ICD formation	[128]	-	-
	Calpains activation	[27, 80]	-	-
Ischemia	TrkB-FL ↓, TrkB-T' or Tc	-	TrkB-FL ↓ [24,27,80]; TrkB-T' or TrkB-Tc ↑ [24,27]; TrkB-T' and TrkB-Tc ↓ [80]	TrkB-FL ↓ and TrkB-Tc ↑ [27]
	TrkB-ICD formation	-	and 42/39 kDa fragments [24]	-
	Calpains activation	-	-	-
Healthy	TrkB-FL ↓, TrkB-T' or Tc ↑	-	[26]	[26]
	TrkB-ICD formation	-	[26]	[26]
	Calpains activation	-	[26]	[26,27]

Abbreviations: BDNF, brain-derived neurotrophic factor. TrkB-FL, full-length tropomyosin receptor kinase B. TrkB-Tc, C-terminal truncated tropomyosin receptor kinase B. TrkB-T', calpain-mediated truncated tropomyosin receptor kinase B. TrkB-ICD, calpain-mediated intracellular fragment from tropomyosin receptor kinase B.

γ-secretase to generate the 39 kDa fragment [24]. Curiously, metalloproteinases can also cleave TrkA, while TrkC is cleaved by caspase-3 [129].

2.7. TrkB-FL cleavage inhibition

Given the loss of neuroprotective TrkB-FL signaling following excitotoxic cleavage, strategies aimed at preserving TrkB-FL integrity have emerged as potential therapeutic approaches. One potential approach involves targeting calpains, the proteases responsible for TrkB-FL cleavage. Inhibiting calpains serves as an upstream strategy to prevent this mechanism and ultimately reduce the burden of epilepsy. Notably, inhibitors targeting the two major calpain isoforms expressed in the brain, namely calpain-1 (or μ-calpain) and calpain-2 (or m-calpain) [130], have been shown to effectively prevent TrkB-FL cleavage in cultured neurons [26,80,85]. Moreover, the administration of low doses of MDL-28170, an inhibitor of both calpains, following SE induction, reduced the frequency of convulsive seizures [131]. In contrast, higher doses of this inhibitor failed to produce similar beneficial effects [131], possibly reflecting the essential role of calpains in cellular homeostasis. Beyond TrkB-FL, calpains cleave multiple substrates, including the p35 protein, mGluR1α, PKC, the NCX3 subtype of the Na^+/Ca^{2+} exchanger (NCX), postsynaptic density protein 95 (PSD-95), the C-terminal region of the GluN2B subunits, and procaspase-3 [132]. Importantly, calpain isoforms exert distinct and sometimes opposing roles: while calpain-1 activation is required for neuroprotective processes, calpain-2 activation is involved in neurodegenerative processes [133]. Therefore, the global inhibition of both calpains may disrupt physiological balance and lead to deleterious outcomes. The selective or partial inhibition of calpain-2 has thus been proposed as a more refined therapeutic strategy. However, although calpain-2 inhibition prevented astroglial and microglial activation, neurodegeneration, and cognitive impairment, it did not reduce or prevent seizure development in an experimental epilepsy model [134]. These findings highlight the need for further studies to clarify the therapeutic potential of calpain-2–targeted interventions in epilepsy.

An alternative strategy to interfere with the calpain-mediated cleavage of TrkB-FL involves the use of a peptide containing a portion of the TrkB-FL sequence. A study implementing this strategy demonstrated effective prevention of TrkB-FL cleavage and subsequent neuroprotection [128]. These results were observed in cultured neurons exposed to excitotoxicity and in a mouse model of ischemia, both pretreated with the peptide [128]. This peptide consisted of the cell-penetrating peptide TAT sequence, derived from the transactivator of transcription (TAT) of the human immunodeficiency virus 1 (HIV-1), fused to a sequence of TrkB-FL. Among several candidates tested, the peptide termed TFL_{457} proved particularly effective by: 1) preventing TrkB-FL cleavage; 2) reducing the formation of a 32 kDa fragment, which resembles the TrkB-ICD identified in the previous study [26], as well as fragments generated by metalloproteinases and γ-secretase; and 3) preserving Tyr^{816} phosphorylation and downstream PLCγ signaling. Notably, the neuroprotective effects of TFL_{457} were independent of direct calpain inhibition and were associated with enhanced retention of TrkB-FL at the plasma membrane following NMDA receptor overactivation. These findings suggest that TFL_{457} may either inhibit TrkB-FL endocytosis, thereby retaining it on the cell surface, where it is less susceptible to degradation, or facilitate TrkB-FL recycling back to the membrane [128]. Curiously, the TAT sequence itself has been shown to bind transcription factors to promoters, modulating chromatin structure and, therefore, stimulating gene expression [135–138]. Whether similar transcriptional effects occur with the TFL_{457} peptide, and which specific genes may be affected, remains to be investigated.

Recent studies have evaluated other peptides containing the TAT sequence and the sequence spanning the cleavage site of TrkB-FL and demonstrated that these domains remain conformationally stable when linked by a lysine–lysine (KK) linker [120]. This TAT-(KK)-TrkB demonstrated efficacy in: 1) preventing TrkB-FL cleavage and TrkB-ICD formation in vitro and in vivo in an AD model; 2) translocating an in vitro model of the blood–brain barrier; 3) preventing synaptotoxicity and preserving synaptic BDNF signaling and function ex vivo; 4) ameliorating synaptic deficits and improving cognitive performance in a transgenic mouse model of AD; and 5) reducing key molecular hallmarks of AD, including phosphorylated tau levels and amyloid-β plaque size, in a transgenic mouse model of AD. Importantly, chronic administration of this peptide did not induce detectable kidney or liver toxicity [120].

3. Conclusion and future perspectives

BDNF/TrkB signaling is clearly involved in neuronal excitability, synaptic plasticity, and circuit remodeling in epilepsy. Although increased BDNF expression is a consistent hallmark of epileptic tissue, clinical and experimental findings indicate that alterations in TrkB signaling cannot be solely explained by changes in BDNF or receptor levels. Instead, the cleavage of TrkB-FL has emerged as a key determinant of dysfunctional neurotrophic signaling in epilepsy.

Seizures, and particularly SE, generate excitotoxic stress that triggers the calpain-dependent cleavage of TrkB-FL, resulting in loss of functional receptors and formation of fragments with kinase activity. Because of this activity, TrkB-ICD is not an inert degradation product; rather, it actively promotes neuronal hyperexcitability, alters gene expression and synaptic processes, providing a direct mechanistic link between seizure-induced excitotoxicity and long-term network instability.

From a translational perspective, TrkB-FL cleavage offers a possible explanation for the apparent discrepancies in TrkB-FL expression reported in human epilepsy and experimental models. By considering this proteolytic processing, these findings may help explain the variability in reported receptor levels across studies and, importantly, highlight TrkB cleavage as a potential therapeutic target. Current antiseizure drugs primarily target ion channels or neurotransmitters and, despite their efficacy in controlling seizures in many patients, generally do not prevent epileptogenesis or modify the underlying progression of epilepsy. Whether currently available antiseizure medications modulate BDNF/TrkB-FL cleavage or TrkB-ICD formation remains largely unexplored in experimental models and in patients with epilepsy. Interestingly, topiramate use was associated with a reduction in a BDNF transcript [68] and valproate ex vivo exposure reduced BDNF and TrkB protein levels [66] in the hippocampi of patients with pharmacoresistant TLE compared to the autopsy control group.

In contrast, strategies aimed at preserving TrkB-FL integrity or preventing TrkB-ICD formation directly target a core pathogenic process associated with seizure-induced plasticity. Nonetheless, further studies are needed to understand the exact impact of TrkB-ICD formation during SE and during epilepsy progression.

The selective modulation of TrkB-FL cleavage, via peptides or similar molecules, may therefore represent a strategy to better understand this mechanism in epilepsy, and possibly a novel disease-modifying strategy to address unmet clinical needs in refractory epilepsy, such as preventing epileptogenesis.

CRediT authorship contribution statement

Leonor Ribeiro-Rodrigues: Writing – original draft, Visualization, Project administration, Investigation, Conceptualization. **Inga Griškova-Bulanova:** Writing – review & editing. **Maria José Diógenes:** Writing – review & editing, Supervision, Funding acquisition. **Sara Xapelli:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

MJD is the author of a patent (Application number: PCT/PT2021/050011; Priority date: 1st April 2020) concerning the prevention of

TrkB-FL cleavage as a therapeutic strategy. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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