The functional and molecular roles of p75 neurotrophin receptor (p75^{NTR}) in epilepsy

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ABSTRACT

Epilepsy is a chronic neurological disorder manifested by recurring unprovoked seizures resulting from an imbalance in the inhibitory and excitatory neurotransmitters in the brain. The process of epileptogenesis involves a complex interplay between the reduction of inhibitory gamma-aminobutyric acid (GABA) and the enhancement of excitatory glutamate. Pro-BDNF/p75^{NTR} expression is augmented in both glial cells and neurons following epileptic seizures and status epileptics (SE). Over-expression of p75^{NTR} is linked with the pathogenesis of epilepsy, and augmentation of pro-BDNF/p75^{NTR} is implicated in the pathogenesis of epilepsy. However, the precise mechanistic function of p75^{NTR} in epilepsy has not been completely elucidated. Therefore, this review aimed to revise the mechanistic pathway of p75^{NTR} in epilepsy.

PLAIN LANGUAGE SUMMARY

Roles of p75 neurotrophin receptor (p75NTR) in epilepsy: Epilepsy is a chronic neurological disorder manifested by recurring unprovoked seizures resulting from an imbalance in the inhibitory and excitatory neurotransmitters in the brain. The process of epileptogenesis involves a complex interplay between the reduction of inhibitory gamma-aminobutyric acid (GABA) and the enhancement of excitatory glutamate. Pro-BDNF/p75NTR expression is augmented in both glial cells and neurons following epileptic seizures and status epileptics (SE). Over-expression of p75NTR is linked with the pathogenesis of epilepsy, and augmentation of pro-BDNF/p75NTR is implicated in the pathogenesis of epilepsy. However, the precise mechanistic function of p75NTR in epilepsy has not been completely elucidated.

KEYWORDS: Epilepsy, p75^{NTR}

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Introduction

The p75 neurotrophin receptor (p75^{NTR}) was initially identified in 1973 as a low-affinity nerve growth factor receptor (LNGFR).[1] The p75^{NTR} is considered to be a functional receptor for various growth factors, such as pro-brain derived neurotrophic factor (pro-BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4).[2] Noteworthy, p75^{NTR} is a member of the superfamily of tumor necrosis factor receptors.[3] It consists of 3 domains, intracellular, transmembrane and extracellular.[2] The tendency of p75^{NTR} is toward dimerization rather than trimerization, owing to the activation of the tyrosine kinase co-receptor.[4] The p75^{NTR} promotes neuronal maturation, differentiation, and survival.[4] The induction of apoptosis by neurotrophins through p75^{NTR} involves the activation of p53, caspase, and c-Jun N-terminal kinase signaling.[5] The engagement of neurotrophins with p75^{NTR} enhances the viability of neurons through the initiation of the nuclear factor kappa B (NF-κB) signaling pathway.[6] p75^{NTR} also involves in interactions with various receptors, such as interaction with the sortilin receptor, which serves as a co-receptor-for-the-functional effects of multiple neurotrophins, including BDNF.[7] Additionally, the pro-BDNF exhibits a more specific binding affinity towards p75^{NTR} in the presence of sortilin receptors.[8] Moreover, the interaction between p75^{NTR} and tropomyosin receptor kinase A (TrkA), resulted in the reduction of p75^{NTR}-induced apoptosis.[9] Also, p75^{NTR} with the

help of the nogo-66 receptor (NgR1) induces apoptosis and inhibits neuronal myelin sheath.[10] The effects of diverse signaling pathways, such as NF-κB, which plays a crucial role in the advancement and progression of neurodegenerative disorders, are mediated by $p75^{NTR}$ [11] (Figure 1).

It has been shown that $p75^{NTR}$ is highly expressed during neuronal development, though these receptors are re-expressed in different pathological conditions including neurodegenerative diseases and epilepsy. For example, toxic peptides and proteins like amyloid beta (Aβ) which accumulated in AD are regarded as a ligand for $p75^{NTR}$ that induces axonal degeneration and synaptic dysfunction.[12] It has been demonstrated that the signaling of $p75^{NTR}$ plays a role in epilepsy, though the precise mechanism was not fully elucidated. Thus, this review tries to show how $p75^{NTR}$ signaling is intricate in epilepsy neuropathology.

Role of $p75^{NTR}$ in epilepsy

Epilepsy is a chronic neurological disorder manifested by recurring unprovoked seizures resulting from an imbalance in the inhibitory and excitatory neurotransmitters in the brain.[13] Epilepsy is classified as a primary (idiopathic) epilepsy when the underlying causes are unidentified.[14] However, secondary (symptomatic) epilepsy is caused by different neurological disorders such as brain injury, brain tumors, neurodegenerative diseases, and infection. Epilepsy is regarded as the fourth common neurological disease affecting more than 50 million in the world. The incidence of epilepsy is 2%–5% in the general population.[15,16] Notably, many signaling pathways are implicated in the pathogenesis of epileptogenesis and epilepsy.[16]

It has been reported that pro-BDNF and mature BDNF (mBDNF) induce divergent physiological responses by activating $p75^{NTR}$ and TrkB respectively.[17] Of note, pro-BDNF/$p75^{NTR}$ is essential for cognitive function, and impairment of this signaling is associated with the development of neurodegenerative and neurodevelopmental disorders.[18] Neuronal cell death in the hippocampus following status epilepticus (SE) is mainly mediated by pro-BDNF/$p75^{NTR}$ signaling since administration of antibodies against pro-BDNF prevents hippocampal cell death following pilocarpine-induced SE.[19] Of interest, proBDNF is localized to mossy fibers and microglia following SE. in addition, $p75^{NTR}$ is momentarily induced primarily in axons and axon terminals following SE, as well as in neuron and astrocyte cell bodies. Furthermore, proBDNF and $p75^{NTR}$ increased independently of cell death and their localization was different depending on the severity of SE. The expression of pro neurotrophin co-receptors, sortilin and sorCS2. Following severe SE, sorCS2, but not sortilin, was elevated in neurons and astrocytes.[20] These data indicate that important differences exist between rat and mouse in the pro-neurotrophin response following SE. Moreover, the proBDNF and $p75^{NTR}$ increase after seizures in the absence of significant cell death suggesting that proneurotrophin signaling may play other roles following SE. However, Pro-BDNF/$p75^{NTR}$ expression is augmented in both glial cells and neurons following seizure and SE in mice regardless of neuronal cell death.[20] This finding signifies that pro-BDNF/$p75^{NTR}$ is linked with epileptogenesis by inhibiting GABA neurotransmission.[20] It has been observed that pro-BDNF/$p75^{NTR}$ signaling inhibits $GABA_A$ receptor and synaptic plasticity though BDNF/TrkB signaling activates GABA long-term potentiation.[21,22] In

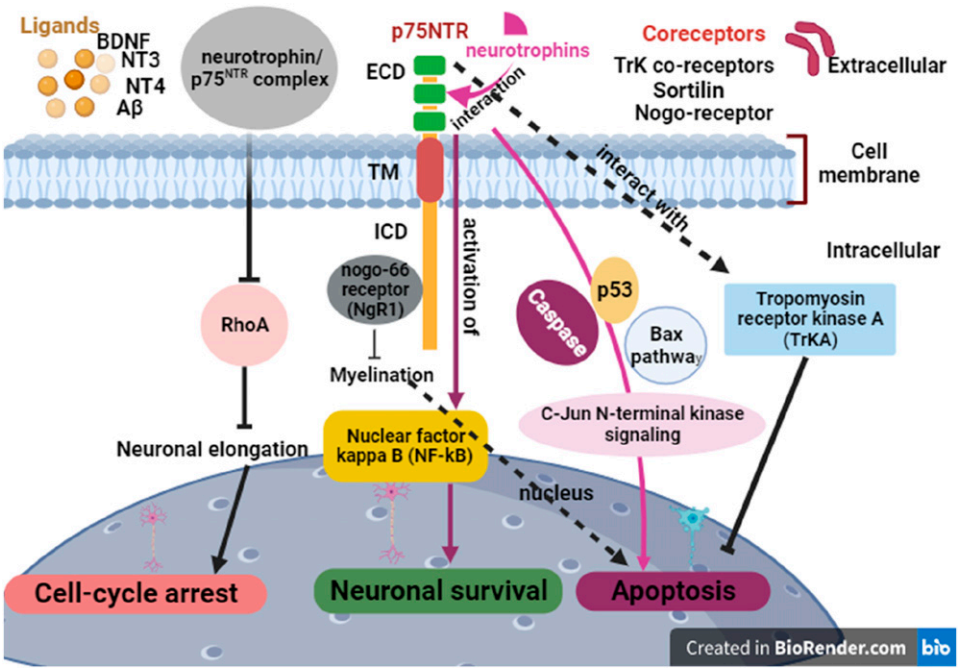

Figure 1. Pathway of $p75^{NTR}$.

addition, pro-BDNF/p75^{NTR} via the Rho-ROCK pathway increases the internalization of the $GABA_A$ receptor and induces degradation of these receptors by the lysosomes leading to disruption of GABAergic neurotransmission in the cortical neurons.[23] In SE, cleavage of BDNF to mBDNF by plasminogen and plasminogen activator is impaired leading to increased pro-BDNF which via the activation of p75^{NTR} induces recurrent seizure by inhibiting GABAergic neurotransmission.[24,25] Mutation of the *plasminogen* gene in mice results in recurrent seizure and SE.[26] Therefore, a deficiency of plasminogen induces severe epilepsy through augmentation of augmentation of pro-BDNF/p75^{NTR}.[26] Consequently, dysregulation of neuronal plasminogen is involved in the pathogenesis of epilepsy.[27] However, many studies confirmed that neuronal plasminogen has little or no role in the pathogenesis of epilepsy.[28,29] Experimental and clinical studies showed that endogenous tissue plasminogen activator (t-PA) was increased following stroke but not intricate in the pathogenesis of epileptogenesis.[28] Likewise, in animal model epilepsy, t-PA plays a little role in the pathogenesis of epileptogenesis.[29] Thus, t-PA is not involved in the pathogenesis of post-stroke epilepsy.

Furthermore, KCC2 which regulates GABAergic neurotransmission and balance between inhibitory/excitatory neural circuits, inhibits epileptogenesis. Down-regulation of KCC2 leads to epileptogenesis in both preclinical and clinical studies.[30,31] Neurons from patients with temporal lobe epilepsy (TLE) had low expression of KCC2.[30] Interestingly, down-regulation of KCC2 following SE persists for weeks leading to the reduction of inhibitory GABAergic neurotransmission and induction of excitatory neurotransmission with subsequent recurrent seizures.[31] Of note, pro-BDNF/p75^{NTR} inhibits the expression of neuronal KCC2 in the TLE animal model.[32] However, BDNF/TrkB promotes the expression of KCC2 in the GABAergic neurons.[33] Indeed, pro-BDNF triggers the expression of p75^{NTR},[23] leading to epileptogenesis by inhibiting GABAergic neurotransmission. Notoriously, GABA-mediated depolarization provokes the expression of p75^{NTR}.[34] These findings illustrated that pro-BDNF/p75^{NTR} is involved in the pathogenesis of epilepsy. Conversely, inhibition of p75^{NTR} before or at the onset of SE did not prevent subsequent seizures in pilocarpine-induced SE in mice.[35] In addition, p75^{NTR} null mice experience higher excitability in the cortical neurons.[36] Thus, pro-BDNF/p75^{NTR} signaling seems to have a neuroprotective against epileptogenesis.[36] A postmortem study involved 18 hippocampal specimens from patients with TLE showed that p75^{NTR} expression was increased in hippocampal neurons contributing to epileptogenesis and neuronal cell deaths.[37] Furthermore, the increased expression of p75^{NTR} in hippocampal neurons of TLE may critically influence neuronal survival during the epileptogenic process.[38] These observations suggest that over-expression of p75^{NTR} is linked with the pathogenesis of severe epilepsy and TLE and SE (Figure 2). However, the mechanistic role of p75^{NTR} and related ligands in epilepsy is not fully elucidated.

Mechanistic pathways of p75^{NTR} in epilepsy

PI3K/Akt

It has been shown that phosphoinositide 3 kinase (PI3K) and protein kinase B also known as the Akt signaling pathway regulate several neurological processes that are critical for the

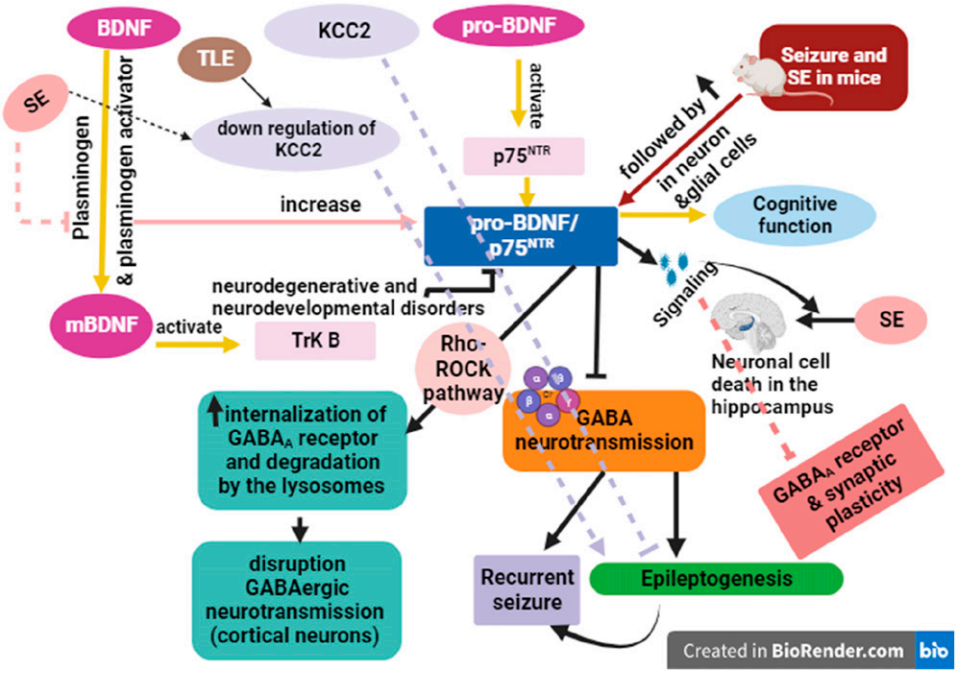

Figure 2. Role of p75^{NTR} in epilepsy.

development of the central nervous system, including neurogenesis, synaptic plasticity, neuronal differentiation, and autophagy.[39] Exaggerated PI3K/Akt is linked with hippocampal neuronal injury in rat epilepsy model, and inhibition of this pathway prevents hippocampal neurodegeneration.[40] Up-regulation of neuronal PI3K is linked with epileptogenesis and induction of epilepsy.[41] Therefore, PI3K inhibitor LY294002 prevents pentylenetetrazole (PTZ)-induced epileptic seizure in zebrafish model.[41] Besides, the Akt signaling pathway promotes epileptic seizure by enhancing the expression of the mechanistic target of rapamycin (mTOR) in the rat TLE model.[42] In this state, Akt inhibitor perifosine attenuates kainic acid (KA)-induced TLE in rats.[42] It has been shown that the PI3K/Akt signaling pathway promotes mTOR-induced epileptogenesis in hippocampal cultured neurons of the post-traumatic epilepsy model.[43] Interestingly, a dual inhibitor of mTOR and PI3K NVP-BEZ235 attenuates the development and progression of epileptic seizures.[43]

On the other hand, $p75^{NTR}$ activation is linked with stimulation of the PI3K/Akt/mTOR signaling pathway. It has been reported that $p75^{NTR}$ signaling increases the activation of the PI3K/Akt signaling pathway.[44] Remarkably, pro-BDNF/$p75^{NTR}$ regulates the excitability of cortical neurons by modulating the PI3K/Akt signaling pathway.[36] However, the preclinical study demonstrated that $p75^{NTR}$ activates autophagy by inhibiting the PI3K/Akt/mTOR signaling pathway.[45] Of note, over-expression of $p75^{NTR}$ during aging promotes the expression of mTOR-mediated synaptic dysfunction in mice.[46] In addition, mTOR inhibitor rapamycine promotes autophagy through a $p75^{NTR}$-dependent pathway.[47] Different studies confirmed that mTOR signaling is highly upregulated in epilepsy.[48,49] It has been observed that the BDNF/$p75^{NTR}$ axis promotes hippocampal glutamatergic excitotoxicity by enhancing the mTOR signaling pathway.[50]

Likewise, The PI3K/Akt/mTOR signaling pathway is modulated by $p75^{NTR}$-mediated enhancement of phosphatase and tensin homolog (PTEN) expression.[47] Of note, PTEN overexpression is associated with glutamate excitotoxicity, neuronal cell death, and epileptogenesis.[51] An experimental study revealed that the administration of PTEN inhibitor picolinate attenuates KA-induced TLE in mice.[51] Interestingly, PTEN variants are associated with drug resistance in patients with focal epilepsy.[52]

Therefore, $p75^{NTR}$ activation is implicated in epileptogenesis by increasing PTEN expression and dysregulation of the PI3K/Akt/mTOR signaling pathway (Figure 3).

Caspase 3 and $p75^{NTR}$

Cysteine proteases, or caspases, play a key role in apoptosis. Caspases are produced as dormant proenzymes and can be classified as effectors (caspase 3, 6, 7), or initiators (caspase 2, 8, 9, 10). The primary mediator of neuronal apoptosis is caspase 3, which also performs non-apoptotic tasks. The physiological functions of caspases are control memory and synaptic functions.[53] The $p75^{NTR}$ activates caspase 3 leading to progressive neuronal injury.[54] Song and coworkers[55] found that PTEN is necessary for shifting the switch between apoptotic and survival pathways in rat brain neurons. Regardless of whether TrkB is activated by BDNF or not, apoptosis is triggered instantly by pro-BDNF and $p75^{NTR}$. The inhibition of PTEN blocks the apoptotic pathway and augments the BDNF/TrkB signaling

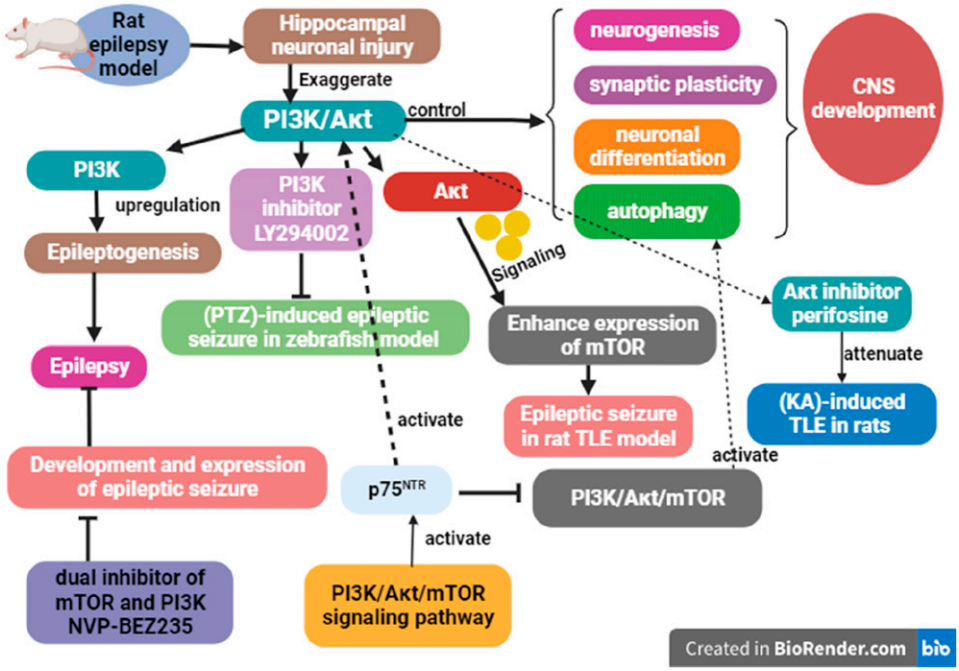

Figure 3. p75NTR activation and epileptogenesis.

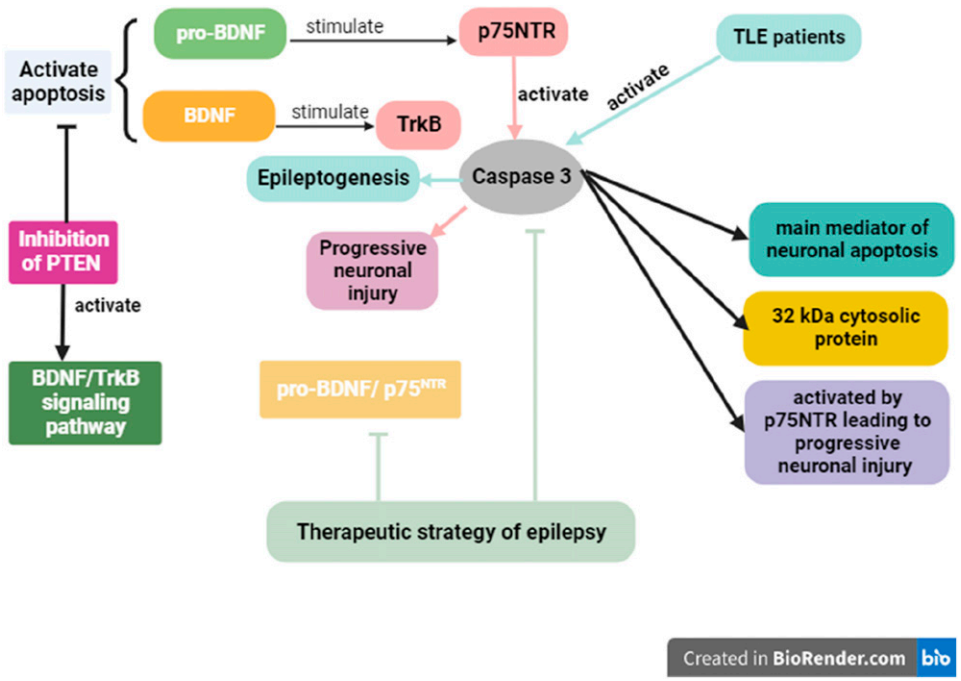

Figure 4. Caspase 3 and p75NTR in epileptogenesis.

pathway. This evidence is corroborated by the confirmation that inhibiting PTEN decreases $p75^{NTR}$-mediated neuronal damage and cell death in rats with pilocarpine-induced epilepsy.[55]

Caspase 3 is extremely activated in patients with TLE[56] signifying that caspase 3 is involved in epileptogenesis, and inhibition of this pathway could be a novel pathway in the management of epilepsy. A previous study indicated that overexpression of caspase 3 is present in resected neocortex from patients with TLE.[57,58] Thus, targeting of caspase 3 may be effective against epileptogenesis. Besides, caspase 3 inhibitors attenuate neuronal loss in traumatic brain injury which is intricate in the development of epilepsy.[59] Different studies reported that pharmacological suppression of caspase 3 was effective in TLE.[60] In this state, pro-BDNF/$p75^{NTR}$ through activation of caspase 3 may lead to neuronal injury, apoptosis, and induction of epileptogenesis.[61] Therefore, direct inhibition of the pro-BDNF/$p75^{NTR}$ signaling pathway or indirect suppression of caspase 3 could be an effective therapeutic strategy in epilepsy (Figure 4).

NF-κB and $p75^{NTR}$

NF-κB, a collective of transcription factors, plays a crucial role in diverse physiological and pathological processes.[62] Two principal pathways of NF-κB have been described, namely the canonical and non-canonical pathways. The canonical NF-κB pathway is initiated in reaction to various external stimuli involved in immune response, inflammation, cell proliferation, and survival.[63] This pathway results in the rapid release of NF-κB and the subsequent inhibition of IκB, which triggers IκB kinase.[64] Higher levels of NF-κB expression trigger the expression of negative regulators like IκBα, which limit the conical NF-κB pathway.[62] However, tumor necrosis factor-alpha (TNF-α) stimulates the non-conical NF-κB pathway by activating NF-κB inducing kinase (NIK).[63] The non-conical NF-κB pathway plays a complex role in the thymus's T cell maturation and immune response regulation.[64] Moreover, an in *vitro* study found that $p75^{NTR}$ activates NF-κB during the apoptosis pathway.[65] It's interesting to note that $p75^{NTR}$ causes cognitive impairment in an animal model study by triggering NF-κB.[6] Furthermore, NF-κB is intricate in the epileptogenesis process by increasing the expression of genes involved in the release of pro-inflammatory cytokines, chemokines, and the development of inflammation.[66] NF-κB is highly expressed in glial cells and neurons, and upregulated of NF-κB is associated with BBB dysfunction and GABA inhibition.[66] NF-κB is highly upregulated in neurons and astrocytes following epileptic seizure within 4 hr in animal epilepsy models.[67] Wang et al.[68] observed that neuronal expression of NF-κB following SE persist for 14 days. Pro-inflammatory cytokines which released from astrocytes and glial cells during epileptic seizure promote the expression of NF-κB and induction of further recurrent epileptic seizure.[69] Therefore, $p75^{NTR}$ via activation of NF-κB may induce the development and progression of epilepsy (Figure 5).

Ras homology family member A/Rho/ROCK and $p75^{NTR}$

RhoA, a member of the Ras homology family, is a small GPTase that plays various cellular roles. It is extensively expressed in neurons and in glial cells.[70] RhoA overexpression is linked to the onset and progression of neurodegenerative

diseases.[71] It has been shown that pro-BDNF-induced $p75^{NTR}$ activation increases RhoA signaling and the expression of apoptosis-mediated proteins like synaptophysin, which causes neuronal apoptosis.[70] Additionally, the $p75^{NTR}$/RhoA signaling pathway is triggered in response to isoflurane, which causes neurotoxicity.[72] Moreover, fingolimod enhances the synaptic plasticity of the hippocampus by suppressing the expression of $p75^{NTR}$ and lowering RhoA signaling in the Huntington disease (HD) mouse model.[73] Identical to Ras, Rho is balanced by regulatory proteins such as GTPase activating protein. ROCK which is also known as Rho kinase is a serine/threonine protein kinase with a molecular weight of 160 kDa. Two types of ROCK are present, ROCK1 which is expressed in non-neuronal tissues and ROCK2 is mainly expressed in neuronal tissues including the brain and spinal cord.[74] Rho-ROCK signaling pathway is implicated in different pathophysiological processes, for example, it inhibits axonal growth during brain injury, and Rho-ROCK inhibitors can improve axonal

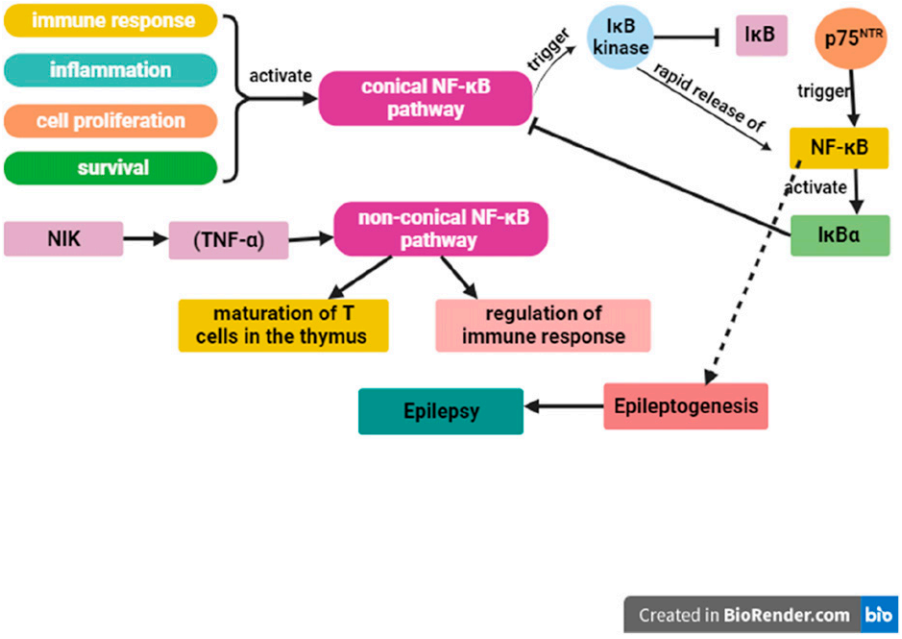

Figure 5. NF-κB and $p75^{NTR}$ in epileptogenesis.

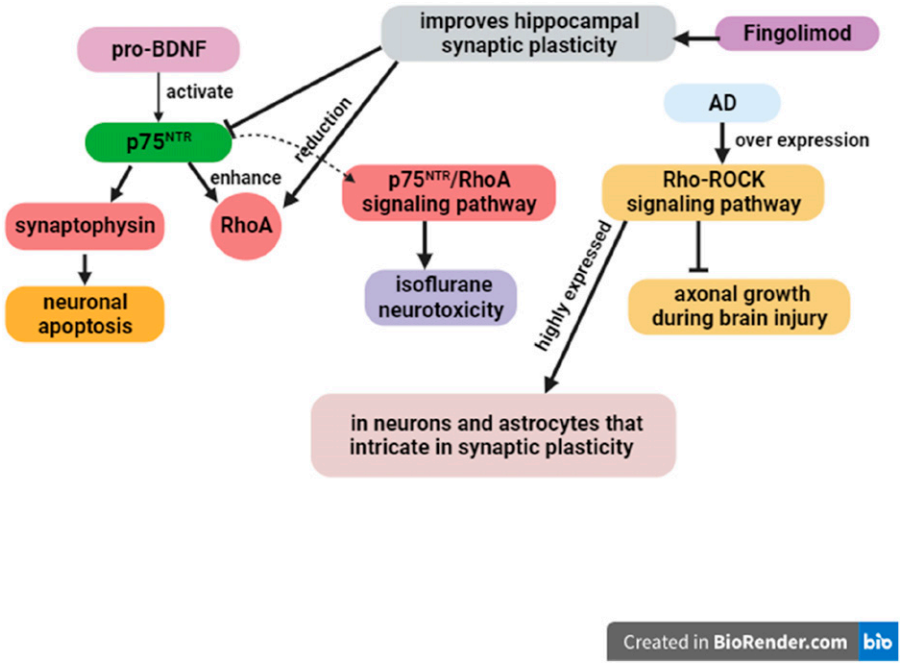

Figure 6. Rho/ROCK and $p75^{NTR}$ in epileptogenesis.

growth.[75] In addition, over-expression of the Rho-ROCK signaling pathway is associated with the development of Alzheimer's disease (AD).[76] Rho-ROCK is highly expressed in neurons and astrocytes that are intricate in synaptic plasticity.[77] Expression of the Rho-ROCK signaling pathway in the hippocampus is augmented following KA-induced SE.[78] It has been shown that Rho-ROCK inhibitor fasudil attenuates KA-induced neuronal injury.[79] Likewise, Rho-ROCK inhibitor Y-27632 decreased the expression of ROCK2 in experimental epileptic seizure in mice.[80] Different studies revealed that $p75^{NTR}$ signaling pathways activate neuronal expression of Rho-ROCK and linked neuronal injury.[81-83] These findings that $p75^{NTR}$ signaling pathway via activation of RhoA and Rho-ROCK signaling increases the risk of epileptic seizure (Figure 6).

Taken together, $p75^{NTR}$ signaling pathway is implicated in epileptogenesis and the pathogenesis of epilepsy by inducing various molecular pathways. Targeting of $p75^{NTR}$ signaling pathway could be a novel pathway in the management of epilepsy.

Conclusions

Epilepsy is a chronic neurological disorder manifested by recurring seizures resulting from an imbalance in the inhibitory and excitatory neurotransmitters in the brain. Many signaling pathways are implicated in the pathogenesis of epileptogenesis and epilepsy. It has been observed that $p75^{NTR}$ a function receptor of proBDNF is dysregulated in epilepsy and implicated in the development and progression of SE and TLE. However, the mechanistic role of $p75^{NTR}$ in the pathogenesis of epilepsy is not completely clarified. Therefore, this review was suggested to review the mechanistic pathway of $p75^{NTR}$ in epilepsy. Interestingly, $p75^{NTR}$ activation is implicated in epileptogenesis by increasing the expression of different signaling pathways. For example, $p75^{NTR}$ increases PTEN expression and dysregulation of the PI3K/Aκt/mTOR signaling pathway that induces epileptogenesis and the induction of epileptic seizure. As well, $p75^{NTR}$ enhances the activity of caspase 3 with subsequent progressive neuronal injury and epileptogenesis. In addition, $p75^{NTR}$ promotes the expression of NF-κB, RhoA and Rho-ROCK signaling which induces the progression of epileptic seizure and the development of TLE. Taken together, the $p75^{NTR}$ signaling pathway is associated with epileptogenesis and the pathogenesis of epilepsy by inducing various molecular pathways. Hence, targeting of $p75^{NTR}$ signaling pathway and associated pathways could be an innovative therapeutic strategy in the management of epilepsy. This review suggests doing preclinical and clinical studies to confirm this scientific claim.

Author contributions

AT, HMA-K, AIA and AkA conceptualized the manuscript, wrote, edited and reviewed the main text and approved the final edition of the manuscript. OE, AAF, FA, HMS and GE-SB prepared the figures, wrote, corrected, amended and approved the final edition of the manuscript.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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