

Synaptic plasticity: one STEP at a time

Steven P. Braithwaite¹, Surojit Paul², Angus C. Nairn³ and Paul J. Lombroso⁴

¹ AGY Therapeutics Inc., 270 E. Grand Avenue, South San Francisco, CA 94080, USA

² Department of Neurology, University of New Mexico, Albuquerque, NM 87131, USA

³ Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06520, USA

⁴ Child Study Center, Yale University School of Medicine, New Haven, CT 06520, USA

Striatal enriched tyrosine phosphatase (STEP) has recently been identified as a crucial player in the regulation of synaptic function. It is restricted to neurons within the CNS and acts by downregulating the activity of MAP kinases, the tyrosine kinase Fyn and NMDA receptors. By modulating these substrates, STEP acts on several parallel pathways that impact upon the progression of synaptic plasticity. Here, we review recent advances that demonstrate the importance of STEP in normal cognitive function, and its possible involvement in cognitive disorders such as Alzheimer's disease.

Introduction

Tyrosine phosphorylation of synaptic receptors and signaling molecules regulates synaptic activity [1,2]. Considerable work has characterized the kinases involved in activity-dependent synaptic plasticity, with relatively less emphasis on the participating protein tyrosine phosphatases (PTPs). However, the identification and characterization of PTPs that participate in this process has begun and several are now known to be specifically expressed within the brain [3].

One of these PTPs was named STEP (for STRiatal-Enriched tyrosine Phosphatase, also known as PTPN5), and recent evidence suggests it is important in synaptic plasticity. The past decade has seen considerable advances in our understanding of the function of STEP, as well as the identification of several target proteins by which STEP controls the development of synaptic plasticity. This review concentrates on three groups of proteins that STEP regulates: the mitogen-activated protein kinases (MAPKs), the tyrosine kinase Fyn, and the NMDA receptor complex. Tyrosine phosphorylation of one member of the MAPK family, the extracellular signal regulated kinase (ERK), is necessary for the expression and maintenance of synaptic plasticity in many brain regions [4], and disruption of the ERK pathway leads to disruption of learning and memory. Activation of the Src family of non-receptor tyrosine kinases is also regulated by tyrosine phosphorylation. One function of these kinases is to phosphorylate NMDA receptors, thereby modulating their channel conductance properties and facilitating their movement to neuronal plasma membranes [2]. This potentiates their activity and is required for the induction of several forms of long-term potentiation (LTP) and long-term depression (LTD) [5,6]. We discuss the properties of STEP that are

necessary for its ability to regulate these three families of proteins and for its role in synaptic function, learning and CNS pathology.

Molecular properties of STEP

STEP is specifically expressed within neurons of the CNS [7]. As its name indicates, the highest expression level is within the striatum [8]. However, more recent work has found that it is expressed at lower levels in multiple regions of the nervous system, including the neocortex, amygdala, hippocampus and embryonic spinal cord [9,10].

PTPs are broadly divided into the receptor-like and the non-receptor, intracellular phosphatases [3,11]. Of the ~100 PTPs identified in the human genome, STEP falls into a small subset of the non-receptor PTPs [12,13]. Based on sequence homology, its closest relatives are HePTP and PTP-SL; these phosphatases are also expressed in a restricted fashion, with HePTP found only in leucocytes and PTP-SL enriched within the cerebellum [14–17].

STEP mRNA is alternatively spliced into two main variants (Figure 1). The protein products are termed STEP₄₆ and STEP₆₁ based on their observed electrophoretic mobility [7,18]. STEP₄₆ is cytosolic, whereas STEP₆₁ is membrane-bound and differs from STEP₄₆ by the presence of an extra 172 amino acids at its N-terminus (Figure 1). STEP₆₁ is not a plasma membrane spanning protein; rather, the N-terminal sequence targets STEP₆₁ to intracellular organelles including the endoplasmic reticulum (ER) and the postsynaptic density [9,18,19]. The orientation of STEP₆₁ on the ER is not currently known: the ability of STEP to regulate cytosolic proteins favors an orientation in which the catalytic domain faces the cytosolic compartment, although additional work is needed to clarify this point. Two additional alternatively spliced variants that lack an active phosphatase domain are expressed [20,21]. The functions of these inactive variants are not known, although it is possible that in the absence of a catalytic domain, they might act as dominant-negative STEP isoforms that compete with the active isoforms for binding to substrates, through binding domains outside of the catalytic domain. In this review, we will concentrate on STEP₄₆ and STEP₆₁ because most of the work to date has studied the function of these two variants.

Both STEP₄₆ and STEP₆₁ have a C-terminal domain of ~280 amino acids that contains a catalytic site with the consensus sequence [I/V]HCxAGxxR[S/T]G (Figure 1). Closer to the N terminal is a kinase-interacting motif (KIM) that is unique to STEP, HePTP and PTP-SL and is the binding site for members of the MAPK family. The

Corresponding author: Braithwaite, S.P. (spbraithwaite@sbcglobal.net);

Lombroso, P.J. (paul.lombroso@yale.edu)

Available online 30 June 2006

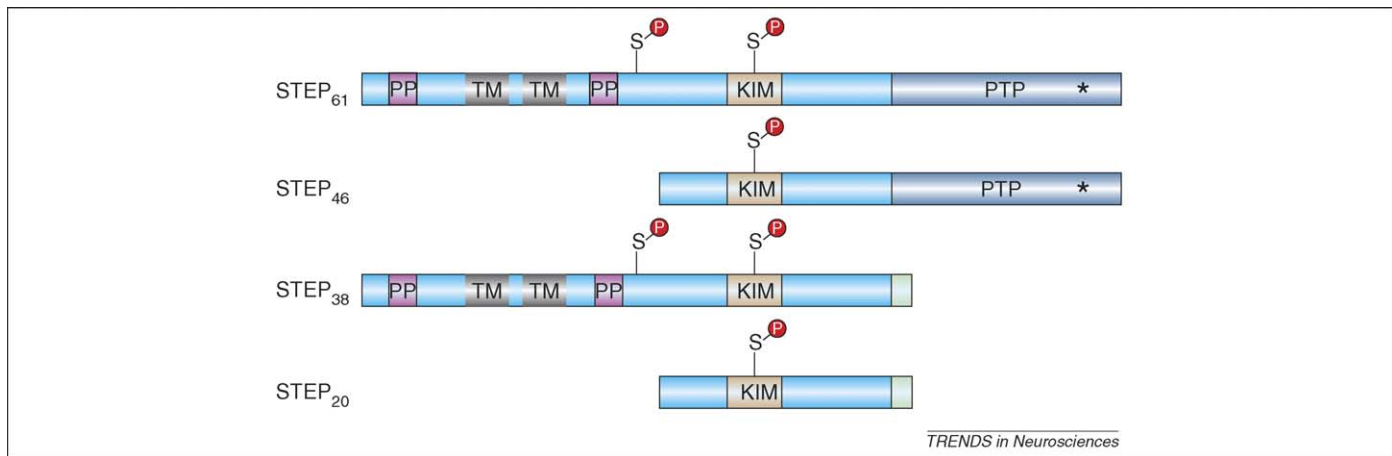


Figure 1. STEP structure. Alternative splicing produces four STEP isoforms. STEP₄₆ and STEP₆₁ contain the catalytic protein tyrosine phosphatase (PTP) domain, which is absent from the other two isoforms, STEP₃₈ and STEP₂₀. STEP₄₆ is cytosolic whereas STEP₆₁ is targeted to the endoplasmic reticulum and the postsynaptic density. These two isoforms differ by an additional 172 amino acids at the N terminus of STEP₆₁. This domain contains two transmembrane (TM) domains and two regions (PP) each formed by a polyproline-rich domain and an adjacent PEST domain. The first polyproline domain interacts with Fyn, whereas the PEST sequences are sites of potential cleavage. Domains that are shared by STEP₄₆ and STEP₆₁ include the binding site for ERK, the kinase-interacting motif (KIM), and the ~280 amino acid PTP domain, which contains an 11-amino-acid catalytic site (asterisks). STEP₆₁ has two serine residues that are phosphorylated by PKA (S), whereas STEP₄₆ contains only the one, within the KIM domain. Phosphorylation within the KIM domain sterically prevents the association of ERK with STEP, and leads to enzyme inactivation. The second serine site in STEP₆₁ is immediately adjacent to a PEST sequence and is thought to facilitate proteolytic cleavage at that site. The functions of STEP₃₈ and STEP₂₀ are not known. These two inactive isoforms might function as dominant-negative variants that compete with the active STEP variants for substrates and, by binding to these substrates, preserve (or prevent) their tyrosine dephosphorylation. Note that these variants also have a novel C-terminal ten-amino-acid sequence (green) that is introduced by alternative splicing and has unknown function.

N-terminal domain of STEP₆₁ contains two polyproline-rich regions. The first of these was shown to mediate, at least in part, the interactions of STEP₆₁ with substrates [22]. Two hydrophobic transmembrane domains and two PEST sequences are also present. The PEST sequences are potential sites for proteolytic cleavage, and two studies have shown that STEP₆₁ is cleaved after hypoxia or anoxia in rat forebrain and after excitotoxic stimulation by glutamate *in vitro* [23,24]; however, whether the PEST sites in STEP₆₁ are the points of cleavage remains to be determined.

Baseline expression of STEP isoforms varies depending on the tissue examined. Thus, the striatum and portions of the amygdala (central nucleus) express both STEP₄₆ and STEP₆₁. The hippocampus, neocortex, spinal cord and lateral aspects of the amygdala express only the larger STEP₆₁ variant. This variation in isoform levels is reflected in the stronger immunohistochemical staining for STEP within the striatum and central nucleus than, for example, within the hippocampus. STEP is normally expressed throughout the length of striatal and central nucleus neurons in a Golgi-like impregnation pattern [9]; thus, the somata, dendritic arbors and axonal processes are all STEP immunoreactive. The projection targets of striatal neurons (globus pallidus and substantia nigra) have only neuritic staining and no detectable STEP immunoreactivity in their cell bodies. This finding indicates that, although the majority of work to date has emphasized the function of STEP postsynaptically, STEP is also present presynaptically and might regulate synaptic transmission through presynaptic mechanisms. For example, ERK has been shown to regulate synapsin I by phosphorylation at key regulatory serine residues [25], and phosphorylation at these sites leads to the movement of synaptic vesicles from a reserve pool to a readily useable pool [26]. The presence of STEP in this compartment would enable inactivation of

ERK and a decrease in the number of vesicles immediately available for fusion. This hypothesis is currently being tested.

Regulation of STEP activity

Studies on the regulation of STEP activity have focused on the striatum, where STEP is expressed in medium spiny neurons that make up ~90% of the neuronal cell types within this brain region [27]. Dopaminergic inputs from the midbrain and glutamatergic afferents from the cortex converge on the spines of these neurons [28], and considerable evidence indicates that the integration of these two synaptic inputs promotes their impact on synaptic function and plasticity. The mechanisms for this integration remain unclear [29] but recent findings suggest that STEP is involved. Stimulation of dopamine D₁ receptors is coupled to adenylyl cyclase through G α_s leading to increased cAMP levels, which in turn activates the cAMP-dependent protein kinase (PKA) pathway. PKA phosphorylates both STEP₄₆ and STEP₆₁ at a regulatory serine residue within their respective KIM domains, and also at a serine residue in the novel 172 amino acid N-terminal domain of STEP₆₁. The effect of phosphorylation is to decrease the enzymatic activity of STEP towards MAPKs (Figure 2). This might be due to a direct effect on the phosphatase catalytic activity, as is suggested by *in vitro* studies [30], which would result in effects on any substrate. Additionally phosphorylation within the KIM domain has been demonstrated to prevent STEP from binding to ERK; however, it remains to be determined whether interactions with other substrates are also affected by phosphorylation within the KIM domain.

Phosphorylation of STEP is stimulated by agonists selective for D₁ dopamine receptors and blocked by D₁ receptor antagonists, but not blocked by D₂ receptor antagonists [31]. Stimulation by glutamate reverses this

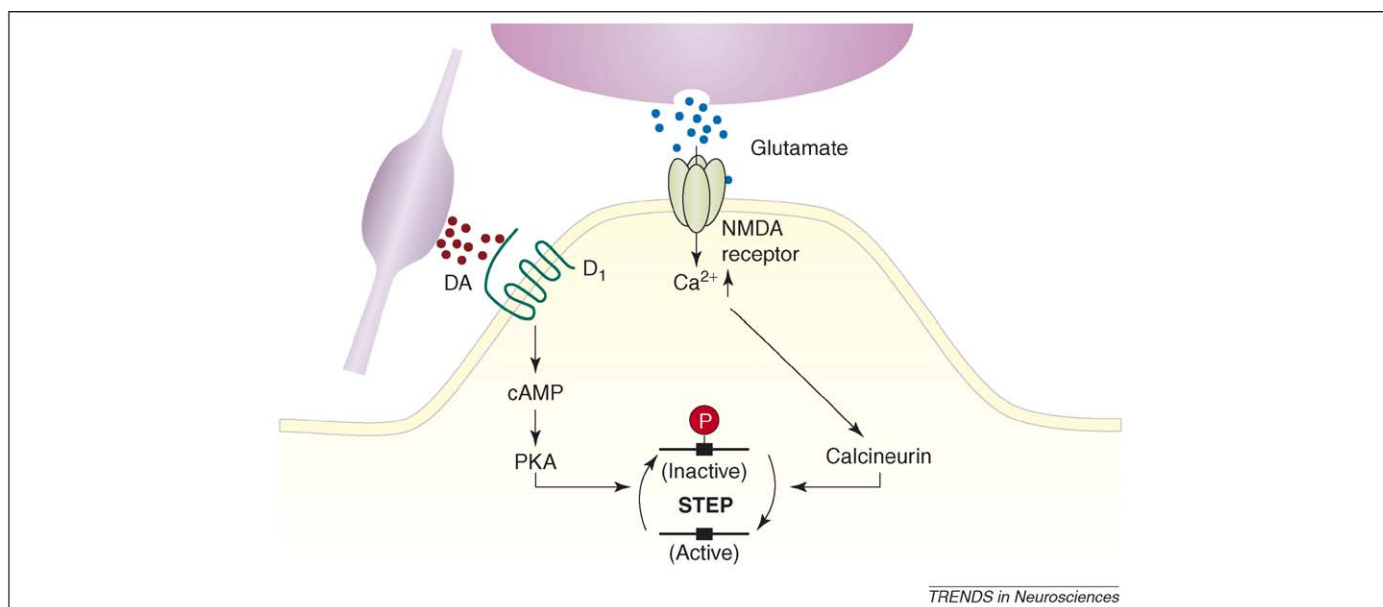


Figure 2. STEP regulation. Stimulation of D₁ receptors by dopamine (DA) leads to cAMP synthesis, PKA activation and phosphorylation of STEP. Phosphorylation of the regulatory serine residue within the KIM domain prevents STEP from interacting with some substrates, such as ERK. Stimulation of NMDA receptors by glutamate enables Ca²⁺ influx and activation of the serine phosphatase calcineurin, leading to dephosphorylation of the regulatory KIM-domain serine residue and thereby activation of STEP.

process and activates STEP. In this reversal, stimulation of NMDA receptors, but not AMPA receptors, results in influx of Ca²⁺ and activation of the serine/threonine phosphatase calcineurin. As a result, STEP is dephosphorylated at the regulatory serine residue of the KIM domain [30]. Furthermore, it has been demonstrated that protein phosphatase 1 (PP-1) can dephosphorylate the regulatory serine residue in the KIM domain of STEP [32] and the highly related HePTP [33].

STEP functions

The specificity of PTPs towards their substrates arises through amino acid modules that target the PTPs to cellular compartments, and additional motifs that lead to their interactions with substrate proteins. As already mentioned STEP, along with its closest relatives HePTP and PTP-SL, contains a KIM domain and this is necessary for binding to the MAPK family members ERK, p38 α , and c-Jun N-terminal kinase (JNK) [33]. STEP, HePTP and PTP-SL all dephosphorylate the regulatory tyrosine residue in the activation loop of MAPKs and thereby inactivate them [30,34–36].

ERK

The ability of STEP to regulate ERK (Figure 3) has been shown in several studies. In corticostriatal cultures, ERK is rapidly activated (within 2 min) in response to stimulation using glutamate, followed by a delayed inactivation of ERK to baseline phosphorylation levels by 20–30 min. This delayed inactivation of ERK is mediated by STEP, through its delayed dephosphorylation within the KIM domain in response to NMDA-receptor-dependent activation of calcineurin [30] (Figure 2). Thus, STEP regulates the temporal profile of ERK activity, and consequently helps to control its translocation to the nucleus and its subsequent downstream nuclear signaling.

STEP is also important in a signal transduction cascade that mediates the effects of psychostimulant drugs on ERK activation [32]. Psychostimulant drugs of abuse exert their addictive effects by increasing extracellular dopamine levels in the nucleus accumbens, where they probably alter the plasticity of corticostriatal glutamate transmission. Cocaine and amphetamine activate ERK in a subset of medium spiny neurons of the dorsal striatum and nucleus accumbens, through the combined action of NMDA and D₁ dopamine receptors. The activation of ERK involves D₁-dependent regulation of PKA, phosphorylation of the regulatory protein dopamine- and cAMP-regulated phosphoprotein with molecular weight 32 kDa (DARPP-32), inhibition of the serine/threonine phosphatase PP-1, and inhibition of STEP. Thus activation of ERK, by a protein phosphatase cascade, detects coincidence of dopamine and glutamate signals converging on accumbens medium spiny neurons and is crucial for long-lasting effects of drugs of abuse.

Recently, a series of *in vivo* investigations directly tested the hypothesis that STEP is involved in regulating synaptic plasticity [37]. ERK activation is required for the consolidation of many forms of long-term memory, including fear conditioning [38]. Mutations of PTPs in their catalytic domain create inactive variants that can be used as substrate-trapping proteins to identify potential substrates. Inactive PTPs bind to their substrates but do not release them, because release requires dephosphorylation of the target protein [39]. A substrate-trapping mutant of STEP₄₆ was made by mutating a required cysteine residue in the catalytic domain to a serine. This STEP variant was made cell permeable by attaching a TAT-peptide to the N terminus. It was infused into the lateral amygdala of rats to determine whether it would bind to ERK, disrupt ERK signaling, and thereby block consolidation of long-term memories after fear conditioning. Animals were trained

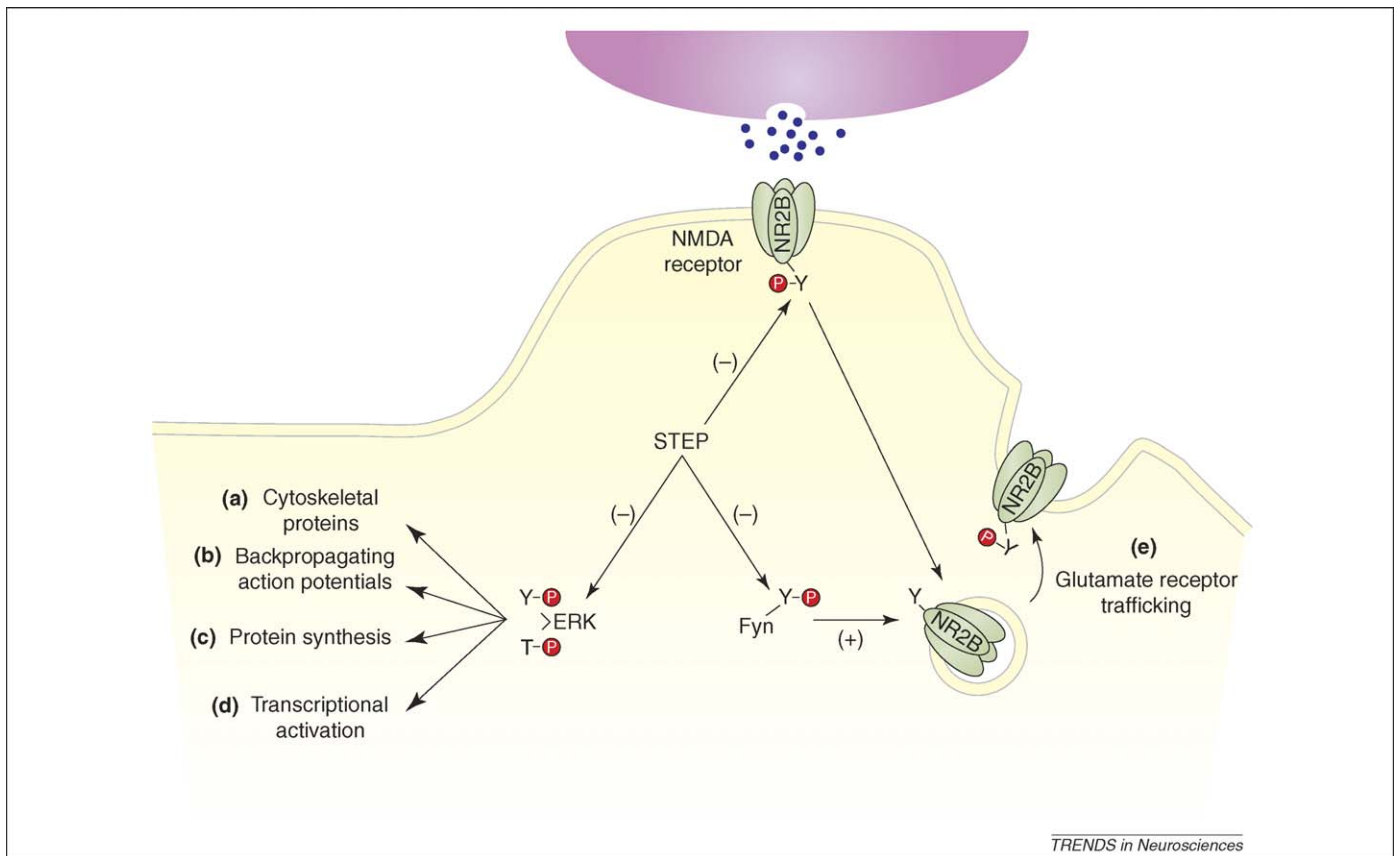


Figure 3. STEP dephosphorylates ERK, Fyn and the NMDA receptor complex. ERK, Fyn and the NR2B subunit of the NMDA receptor are potential STEP substrates. Active ERK is required for synaptic plasticity in all brain regions tested to date. In its activated state, ERK phosphorylates cytoskeletal proteins (a), regulates backpropagating action potentials (b), stimulates protein synthesis (c), and activates transcription (d). These processes work in parallel to promote synaptic plasticity. Fyn activation has also been implicated in synaptic plasticity through various mechanisms including regulation of glutamate receptor trafficking (e). Tyrosine phosphorylation of the NR2B subunit of the NMDA receptor results in exocytosis of NMDA-receptor-containing endosomes.

on a standard protocol where a shock is paired with an acoustic cue. Short-term memory was not affected in these animals, implying that the substrate-trapping TAT-STEP protein did not block the acquisition of this form of memory. However, 24 h after fear conditioning, long-term memory was disrupted, indicating an effect on the consolidation of fear memories.

There were two striking observations in that study. The first was the rapidity of ERK activation after fear conditioning. Phosphorylated ERK (pERK) was detected in lateral amygdala neurons within five minutes of training; its levels returned to baseline by 15 min, and then increased again by one hour. The initial activation of ERK is thought to occur through the convergence onto lateral amygdala neurons of auditory thalamic inputs in response to the conditioning stimulus (tone) and of somatosensory thalamic inputs in response to the unconditioned stimulus (electrical foot shock). Both inputs are required for the establishment of LTP in the lateral amygdala and the consolidation of fear conditioning [40,41].

The second major finding was that activation of ERK was followed within an additional few minutes by the *de novo* translation of STEP [37]. This translation was blocked by anisomycin, was not affected by actinomycin D, and was blocked by inhibitors of MAPK. Importantly, neither shock alone nor tone alone led to ERK activation or STEP translation. Within minutes after the *de novo*

synthesis of STEP, pERK levels returned to baseline levels. These results support a feedback model by which STEP regulates the duration of ERK activity. Additional modulatory inputs are likely to be involved. For example, if dopamine input arrives to these same neurons, then STEP will be phosphorylated and no longer interact with ERK, leading to a more persistent pERK signal. Additional studies are needed to determine whether the infused TAT-STEP that prevented the consolidation of fear conditioning did so through its ability to block ERK signaling only, or whether it also disrupts other components of synaptic plasticity, through the regulation of STEP substrates such as Fyn or NMDA receptors.

Fyn

As already mentioned, mutations of PTPs in their catalytic domain create inactive variants that can be used as substrate-trapping proteins. Such an inactive STEP protein was used to identify the non-receptor tyrosine kinase Fyn as a second STEP substrate [22] (Figure 3). STEP interacts with Fyn through its KIM domain, although the first polyproline sequence present in STEP61 is also involved in Fyn binding [22]. Interestingly, two other Src-family members (Src and Lyn) and Pyk2 did not interact directly with STEP under the conditions used in this study [22]. Two tyrosine residues are phosphorylated in Src-family non-receptor kinases, and the enzymatic activity of these

proteins depends on which tyrosine is phosphorylated. STEP specifically catalyzes the dephosphorylation of Fyn at Tyr420, leading to inactivation. Conversely, a second PTP (PTP α) dephosphorylates Fyn at Tyr531, leading to activation [42,43].

NMDA receptors

The NMDA receptor is a third potential STEP substrate. The NR1 subunit was initially shown to associate with STEP through co-immunoprecipitation experiments using hippocampal tissue [10], and more recently it has been shown that NMDA receptor subunits and STEP interact directly [44]. STEP regulates NMDA receptor trafficking by controlling the level of tyrosine phosphorylation of the NR2B subunit [45]. Phosphorylation of NR2B at Tyr1472 by Src-family members, including Fyn, is required for the movement of NMDA receptors into membranes [46,47]. Dephosphorylation of the NR2B subunit at this residue leads to endocytosis of NMDA receptors through a mechanism mediated by clathrin and adaptor protein 2 [48]. Current studies are investigating whether this is a direct effect, through dephosphorylation of the NMDA receptor by STEP, or an indirect effect, through the ability of STEP to reduce Fyn activity and thus decrease NMDA receptor phosphorylation levels, or whether both mechanisms work together in a cooperative fashion (Figure 4).

An initial electrophysiological study looked at the ability of STEP to regulate NMDA receptor channel properties [10]. STEP affects the function of synaptic NMDA receptors in both spinal cord cultures and hippocampal CA1 pyramidal neurons. Exogenously applied STEP decreased the open probability and mean channel-open time of NMDA receptors in single-channel recordings from excised patches of spinal cord neurons [10]. Furthermore, infusion of a functionally inhibitory STEP antibody increased the NMDA-receptor-mediated component of synaptic responses. Because NMDA receptors are crucial for the induction of LTP, it was important to examine the role of STEP in this form of synaptic plasticity [10]. Microinfusion of active STEP protein into the postsynaptic neuron blocked LTP induction at hippocampal Schaffer collateral CA1 synapses. Conversely, infusion of the functionally inhibitory antibody caused an increase in basal synaptic transmission, thereby occluding LTP induction. Thus, STEP seems to directly affect the conductance properties of NMDA receptors in addition to regulating NMDA receptor trafficking, and together these mechanisms oppose the development of synaptic plasticity.

Significance of STEP in pathological states

Recent studies have linked STEP to the cognitive decline observed in Alzheimer's disease [45]. The abnormal

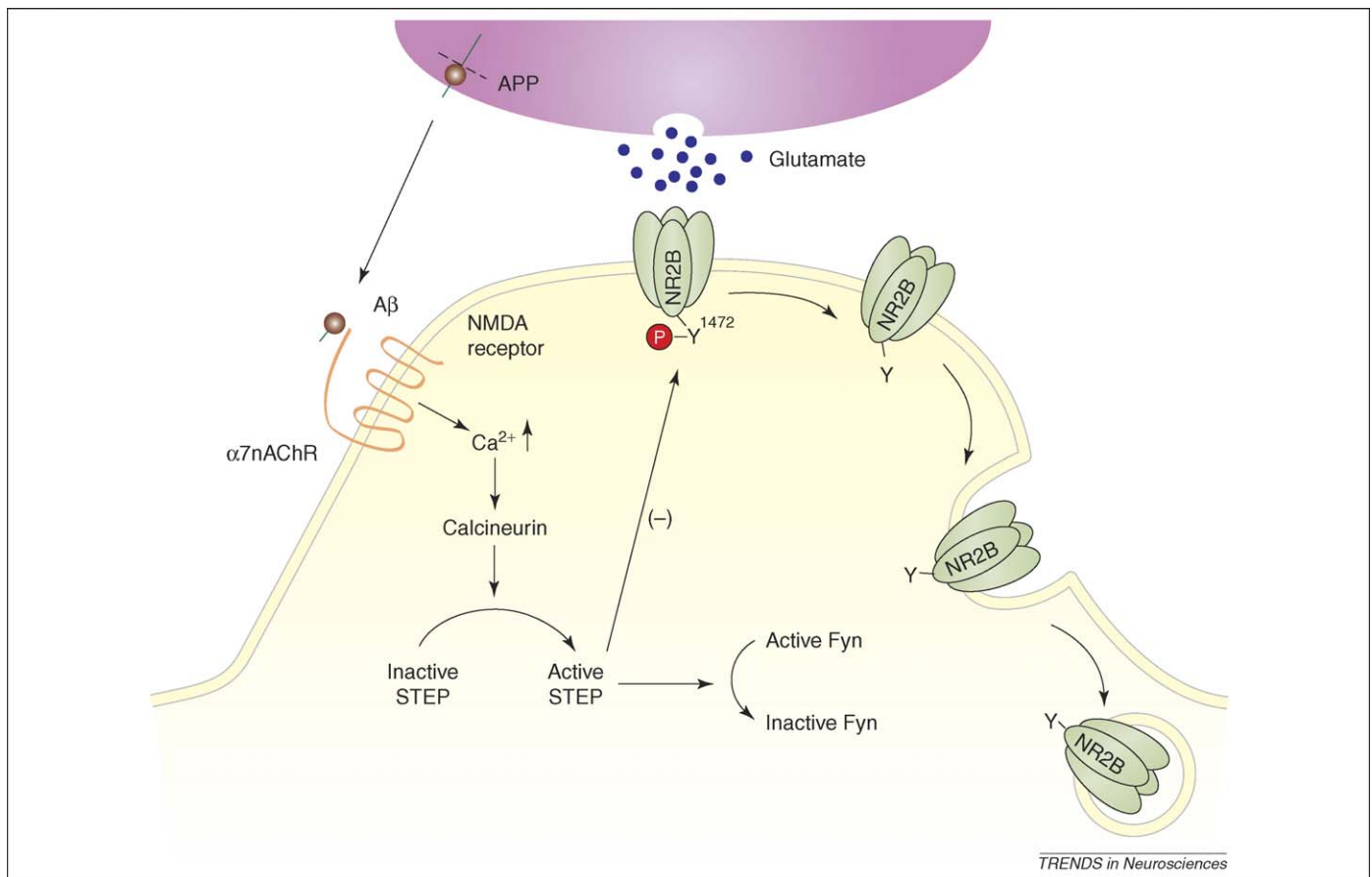


Figure 4. STEP activation might lead to abnormal NMDA receptor endocytosis in Alzheimer's disease. A β -peptide binding to the α 7 nicotinic ACh receptor (α 7nAChR) leads to Ca²⁺ influx, calcineurin activation and STEP dephosphorylation. Dephosphorylation activates STEP, which in turn inactivates Fyn. Fyn has been implicated in the phosphorylation of a regulatory tyrosine residue (Tyr1472) on the NR2B subunit of the NMDA receptor that leads to exocytosis of this receptor. In the absence of Fyn-mediated tyrosine phosphorylation, the NMDA receptor is internalized by endocytosis. Active STEP opposes trafficking to the membrane by dephosphorylating Fyn, and also by dephosphorylating the Tyr1472 site on the NR2B subunit.

secretion of β -amyloid peptide ($A\beta$) has been implicated in Alzheimer's disease, and the appearance of plaques and neurofibrillary tangles have been thought to be a pathogenic cause of the disorder. A second model posits that soluble $A\beta$ interferes with synaptic function itself even before plaques and neurofibrillary tangles become apparent [49,50].

Snyder *et al.* [45] directly tested the synaptic hypothesis of Alzheimer's disease by asking whether $A\beta$ might disrupt NMDA receptor trafficking. $A\beta$ promoted the endocytosis of NMDA receptors in hippocampal cultures without affecting the total level of these receptors. Moreover, similarly decreased expression of glutamate receptors was found on neuronal plasma membranes in a mouse model of Alzheimer's disease that secretes high levels of $A\beta$. As already mentioned, exocytosis and endocytosis of NMDA receptors are regulated, in part, by tyrosine phosphorylation of the NR2B subunit. $A\beta$ -induced endocytosis of NMDA receptors was blocked by preincubation of hippocampal cultures with the substrate-trapping TAT-STEP protein. This implies that STEP is normally involved in the endocytosis of glutamate receptors, and that it is inappropriately activated by $A\beta$.

The study went on to determine the signaling pathway by which $A\beta$ -induced endocytosis occurred (Figure 4). $A\beta$ was found to bind the $\alpha 7$ nicotinic ACh receptor ($\alpha 7nAChR$), leading to Ca^{2+} influx and activation of calcineurin. Calcineurin activity resulted in dephosphorylation of the regulatory serine residue within the KIM domain of STEP, thereby activating it. Active STEP could then dephosphorylate Fyn and/or NR2B, promoting endocytosis of NMDA receptors. A second study has also implicated STEP in the actions of $A\beta$. In a different transgenic mouse model of Alzheimer's disease, increased levels of $\alpha 7nAChR$, decreased Fyn activity and increased STEP protein levels were found in the dentate gyrus [51].

It remains to be determined exactly how the substrate-trapping TAT-STEP prevents NMDA receptor endocytosis. Given that it is a substrate-binding protein, one possible model is that TAT-STEP binds to Tyr1472 and blocks normal dephosphorylation of that site. The increased tyrosine phosphorylation of NR2B would promote its localization at the plasma membrane. This model fits with the hypothesis that one of the earliest pathological events in Alzheimer's disease is tyrosine-dephosphorylation-mediated endocytosis of glutamate receptors, and that this process is involved in the progressive cognitive loss in affected patients. Because STEP is an integral part of the signaling pathway between $A\beta$ and NMDA receptors, inhibiting STEP activity is a potential avenue for new therapeutic agents in the treatment of Alzheimer's disease.

Concluding remarks

STEP regulates the activity of the MAPKs, Fyn and NMDA receptors, and by regulating these substrates it opposes the development of synaptic plasticity. Future work will determine whether STEP also has a role in memory consolidation in brain regions outside of the amygdala. Additional studies should focus on the contribution of STEP to CNS disorders, because of its high levels of expression in the striatum and the crucial nature of its substrates. As Confucius said, 'A journey of a thousand miles begins with

a single step.' The possibilities are only just beginning to be recognized, and clarifying the roles of STEP will be an exciting journey.

References

- Soderling, T.R. and Derkach, V.A. (2000) Postsynaptic protein phosphorylation and LTP. *Trends Neurosci.* 23, 75–80
- Salter, M.W. and Kalia, L.V. (2004) Src kinases: a hub for NMDA receptor regulation. *Nat. Rev. Neurosci.* 5, 317–328
- Paul, S. and Lombroso, P.J. (2003) Receptor and nonreceptor protein tyrosine phosphatases in the nervous system. *Cell. Mol. Life Sci.* 60, 2465–2482
- Sweatt, J.D. (2004) Mitogen-activated protein kinases in synaptic plasticity and memory. *Curr. Opin. Neurobiol.* 14, 311–317
- Nicoll, R.A. (2003) Expression mechanisms underlying long-term potentiation: a postsynaptic view. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 358, 721–726
- Collingridge, G.L. *et al.* (2004) Receptor trafficking and synaptic plasticity. *Nat. Rev. Neurosci.* 5, 952–962
- Lombroso, P.J. *et al.* (1991) Molecular characterization of a protein tyrosine phosphatase enriched in striatum. *Proc. Natl. Acad. Sci. U. S. A.* 88, 7242–7246
- Lombroso, P.J. *et al.* (1993) A protein tyrosine phosphatase expressed within dopaminergic neurons of the basal ganglia and related structures. *J. Neurosci.* 13, 3064–3074
- Boulanger, L.M. *et al.* (1995) Cellular and molecular characterization of a brain-enriched protein tyrosine phosphatase. *J. Neurosci.* 15, 1532–1544
- Pelkey, K. *et al.* (2002) Tyrosine phosphatase STEP is a tonic brake on induction of long-term potentiation. *Neuron* 34, 127–138
- Stoker, A.W. (2005) Protein tyrosine phosphatases and signalling. *J. Endocrinol.* 185, 19–33
- Andersen, J.N. *et al.* (2004) A genomic perspective on protein tyrosine phosphatases: gene structure, pseudogenes, and genetic disease linkage. *FASEB J.* 18, 8–30
- Alonso, A. *et al.* (2004) Protein tyrosine phosphatases in the human genome. *Cell* 117, 699–711
- Zanke, B. *et al.* (1992) Cloning and expression of an inducible lymphoid-specific, protein tyrosine phosphatase (HePTPase). *Eur. J. Immunol.* 22, 235–239
- Sharma, E. and Lombroso, P.J. (1995) A neuronal protein tyrosine phosphatase induced by nerve growth factor. *J. Biol. Chem.* 270, 49–53
- Hendriks, W. *et al.* (1995) A novel receptor-type protein tyrosine phosphatase with a single catalytic domain is specifically expressed in mouse brain. *Biochem. J.* 305, 499–504
- Chirivi, R.G. *et al.* (2004) Characterization of multiple transcripts and isoforms derived from the mouse protein tyrosine phosphatase gene *Ptpr*. *Genes Cells* 9, 919–933
- Bult, A. *et al.* (1996) STEP61: A new member of a family of brain-enriched PTPs is localized to the ER. *J. Neurosci.* 16, 7821–7831
- Oyama, T. *et al.* (1995) Immunocytochemical localization of the striatal enriched protein tyrosine phosphatase in the rat striatum: EM study. *Neuroscience* 69, 869–880
- Bult, A. *et al.* (1997) STEP: A family of brain enriched PTPs: Alternative splicing produces transmembrane, cytosolic and truncated isoforms. *Eur. J. Cell Biol.* 72, 337–344
- Sharma, E. *et al.* (1995) Identification of two alternatively spliced transcripts of STEP: a subfamily of brain-enriched protein tyrosine phosphatases. *Mol. Brain Res.* 32, 87–93
- Nguyen, T.H. *et al.* (2002) Striatal enriched phosphatase 61 (STEP61) dephosphorylates Fyn at phosphotyrosine 420. *J. Biol. Chem.* 277, 24274–24279
- Gurd, J. *et al.* (1999) Hypoxia-ischemia in perinatal rat brain induces the formation of a low molecular weight isoform of the protein tyrosine phosphatase, STEP. *J. Neurochem.* 73, 1990–1995
- Nguyen, T.H. *et al.* (1999) Calcium-dependent cleavage of striatal enriched tyrosine phosphatase (STEP). *J. Neurochem.* 73, 1995–2001
- Jovanovic, J.N. *et al.* (1996) Neurotrophins stimulate phosphorylation of synapsin I by MAP kinase and regulate synapsin I-actin interactions. *Proc. Natl. Acad. Sci. U. S. A.* 93, 3679–3683
- Kushner, S.A. *et al.* (2005) Modulation of presynaptic plasticity and learning by the H-ras/extracellular signal-regulated kinase/synapsin I signaling pathway. *J. Neurosci.* 25, 9721–9734

- 27 Packard, M.G. and Knowlton, B.J. (2002) Learning and memory functions of the basal ganglia. *Annu. Rev. Neurosci.* 25, 563–593
- 28 Kotter, R. (1994) Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum. *Prog. Neurobiol.* 44, 163–196
- 29 Cepeda, C. and Levine, M.S. (1998) Dopamine and *N*-methyl-D-aspartate receptor interactions in the neostriatum. *Dev. Neurosci.* 20, 1–18
- 30 Paul, S. *et al.* (2003) NMDA-mediated activation of the protein tyrosine phosphatase, STEP, regulates the duration of ERK signaling. *Nat. Neurosci.* 6, 34–42
- 31 Paul, S. *et al.* (2000) Dopamine/D1 receptor mediates the phosphorylation and inactivation of the protein tyrosine phosphatase, STEP, through a PKA-mediated pathway. *J. Neurosci.* 20, 5630–5638
- 32 Valjent, E. *et al.* (2004) Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. *Proc. Natl. Acad. Sci. U. S. A.* 102, 491–496
- 33 Nika, K. *et al.* (2004) Hematopoietic protein tyrosine phosphatase (HePTP) phosphorylation by cAMP-dependent protein kinase in T cells: dynamics and subcellular location. *Biochem. J.* 378, 335–342
- 34 Pulido, R. *et al.* (1998) PTP-SL and STEP protein tyrosine phosphatases regulate the activation of the extracellular signal-regulated kinases ERK1 and ERK2 by association through a kinase interaction motif. *EMBO J.* 17, 7337–7350
- 35 Saxena, M. *et al.* (1999) Inhibition of T cell signaling by mitogen-activated protein kinase-targeted hematopoietic tyrosine phosphatase (HePTP). *J. Biol. Chem.* 274, 11693–11700
- 36 Zuniga, A. *et al.* (1999) Interaction of mitogen-activated protein kinases with the kinase interaction motif of the tyrosine phosphatase PTP-SL provides specificity and retains ERK2 in the cytoplasm. *J. Biol. Chem.* 274, 21900–21907
- 37 Paul, S. *et al.* (2004) Disruption of fear conditioning by STEP, a striatal enriched phosphatase, through the regulation of MAP kinase. In *2004 Abstract Viewer and Itinerary Planner*, program number 632.11, Society for Neuroscience, online (<http://sfn.scholarone.com/>)
- 38 Schafe, G.E. *et al.* (2000) Activation of ERK/MAP kinase in the amygdala is required for memory consolidation of Pavlovian fear conditioning. *J. Neurosci.* 20, 8177–8187
- 39 Flint, A. *et al.* (1997) Development of substrate trapping mutants to identify physiological substrates of PTPs. *Proc. Natl. Acad. Sci. U. S. A.* 94, 1680–1685
- 40 Schafe, G.E. and LeDoux, J.E. (2000) Memory consolidation of auditory pavlovian fear conditioning requires protein synthesis and protein kinase A in the amygdala. *J. Neurosci.* 20, RC96
- 41 Blair, H.T. *et al.* (2001) Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. *Learn. Mem.* 8, 229–242
- 42 Zheng, X.M. *et al.* (1992) Cell transformation and activation of pp60-c-src by overexpression of a protein tyrosine phosphatase. *Nature* 359, 336–339
- 43 Bhandari, V. *et al.* (1998) Physical and functional interactions between receptor-like protein-tyrosine phosphatase α and p59fyn. *J. Biol. Chem.* 273, 8691–8698
- 44 Braithwaite, S.P. *et al.* Regulation of NMDA receptor trafficking and function by striatal enriched tyrosine phosphatase (STEP) *Eur. J. Neurosci.* (in press)
- 45 Snyder, E.M. *et al.* (2005) Regulation of NMDA receptor trafficking by β -amyloid. *Nat. Neurosci.* 8, 1051–1058
- 46 Dunah, A.W. *et al.* (2004) Dopamine D1-dependent trafficking of striatal *N*-methyl-D-aspartate glutamate receptors requires Fyn protein tyrosine kinase but not DARPP-32. *Mol. Pharmacol.* 65, 121–129
- 47 Cheung, H.H. and Gurd, J.W. (2001) Tyrosine phosphorylation of the *N*-methyl-D-aspartate receptor by exogenous and postsynaptic density-associated Src-family kinases. *J. Neurochem.* 78, 524–534
- 48 Lavezzari, G. *et al.* (2003) Differential binding of the AP-2 adaptor complex and PSD-95 to the C-terminus of the NMDA receptor subunit NR2B regulates surface expression. *Neuropharmacology* 45, 729–737
- 49 Walsh, D.M. *et al.* (2002) Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation *in vivo*. *Nature* 416, 535–539
- 50 Kamenetz, F. *et al.* (2003) APP processing and synaptic function. *Neuron* 37, 925–937
- 51 Chin, J. *et al.* (2005) Fyn kinase induces synaptic and cognitive impairments in a transgenic mouse model of Alzheimer's disease. *J. Neurosci.* 25, 9694–9703

TINS Editorial Policy

Trends journals are indispensable reading for anyone interested in the life-sciences. At the heart of the journal are authoritative overview articles which, through synthesis and discussion, present an integrated view of the latest research. TINS Reviews and Opinions are written by leading authors, and the majority are commissioned by the editor, but we occasionally consider proposals.

- **Review** articles provide clear, concise, well illustrated and balanced discussions of recent advances, synthesizing the primary literature and identifying important trends and key questions for ongoing research.
- **Opinion** articles are special reviews designed to stimulate debate and cover controversial and emerging areas of research, and to present new hypotheses relating to important outstanding questions in neuroscience.
- **Research Focus** articles provide a short but critical analysis of recent primary research papers, and are restricted to 1000 words plus one figure.

All submitted articles are thoroughly peer reviewed, and only articles that reach the required standard are published.

Authors wishing to contribute to TINS: please submit a point-by-point outline of your intended article, together with key references that illustrate both why you would be our first author of choice for such an article and the breadth of intended source material (to tins@elsevier.com).