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Tyrosine phosphorylation of glutamate receptors by non-receptor tyrosine kinases: roles in depression-like behavior

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Abstract

Several key members of the non-receptor tyrosine kinase (nRTK) family are abundantly present within excitatory synapses in the mammalian brain. These neuron-enriched nRTKs interact with glutamate receptors and phosphorylate the receptors at tyrosine sites. The *N*-methyl-D-aspartate receptor is a direct substrate of nRTKs and has been extensively investigated in its phosphorylation responses to nRTKs. The α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor is the other glutamate receptor subtype that is subject to nRTK-mediated tyrosine phosphorylation. Recently, group I metabotropic glutamate receptors (mGluR1/5) were found to be sensitive to nRTKs. Robust tyrosine phosphorylation may occur in C-terminal tails of mGluR5. Tyrosine phosphorylation of glutamate receptors is either constitutive or induced activity-dependently by changing cellular and/or synaptic input. Through inducing tyrosine phosphorylation, nRTKs regulate trafficking, subcellular distribution, and function of modified receptors. Available data show that nRTK-glutamate receptor interactions and tyrosine phosphorylation of the receptors undergo drastic adaptations in mood disorders such as major depressive disorder. The remodeling of the nRTK-glutamate receptor interplay contributes to the long-lasting pathophysiology and symptomology of depression. This review summarizes the recent progress in tyrosine phosphorylation of glutamate receptors and analyzes the role of nRTKs in regulating glutamate receptors and depression-like behavior.

Keywords

Excitatory amino acid; AMPA; NMDA; mGluR; synaptic plasticity; LTP; LTD; Src; Fyn

Introduction

There are two classes of glutamate receptors in the central nervous system: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). The former is a ligand-gated ion channel and mediates fast synaptic transmission, while the latter is a family of G protein-coupled receptors (GPCRs) and acts as a modulator in a variety of cellular and synaptic activities [1,2]. iGluRs include α-amino-3-hydroxy-5-

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Conflict of interest statement

The authors declare no conflict of interest.

methylisoxazole-4-propionic acid receptors (AMPARs), *N*-methyl-D-aspartate receptors (NMDARs), and kainate receptors[1]. These receptors form heteromers or homomers to gain full function. Eight mGluR subtypes (mGluR1-8) are so far cloned. They are grouped into three functional groups based on their pharmacological profiles and signaling connections. Among these groups, group I mGluRs (mGluR1/5) have been most thoroughly investigated for their roles and regulatory mechanisms [2]. Stimulation of Gαq-associated mGluR1/5 activates phospholipase Cβ1. Activated phospholipase Cβ1 hydrolyzes phosphoinositide into inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). By triggering IP_3- and DAG-sensitive signaling pathways, mGluR1/5 regulate cellular and synaptic responses to different stimuli.

Both iGluRs and mGluRs are subject to a posttranslational modification, i.e., phosphorylation. Robust phosphorylation usually occurs at specific sites in the intracellular domains, especially the C-terminal (CT) tail. By altering the basal level of phosphorylation or by inducing phosphorylation at a specific residue in a receptor, various protein kinases control biochemical and functional properties of modified receptors [3,4]. A notable protein kinase family is the non-receptor tyrosine kinases (nRTKs) that catalyze phosphorylation at the tyrosine residue [5]. There are a large number of nRTKs that are classified into several subfamilies [5]. Several key nRTKs, including the Src family members (Src, Fyn, Yes, Lyn and Lck) and the focal adhesion kinase (Fak) family members (Fak and Pyk2), are highly expressed in the brain [6-8]. Among these brain-enriched nRTKs, Src and Fyn are particular interesting due to their abundance at excitatory synapses and well demonstrated roles in phosphorylating and regulating glutamate receptors [9,10]. This review describes the nRTK interaction with glutamate receptors and analyzes roles of nRTKs in the regulation of iGluRs and group I mGluR activities with a focus on recent progress. In addition, emerging evidence supports implications of tyrosine phosphorylation of glutamate receptors in mood disorders. We thus analyzed the linkage of glutamate receptor tyrosine phosphorylation to mood disorders with a focus on depression.

Tyrosine phosphorylation of iGluRs by nRTKs

iGluRs become functional after they are assembled into tetrameric structures [1]. Functional NMDARs contain obligatory GluN1 (formerly known as NR1) and modulatory GluN2 subunits, mainly GluN2A (NR2A) and GluN2B (NR2B) [1]. AMPARs form functional channels when four subunits (GluA1-4, previously named GluR1-4) are assembled into a dimer-of-dimers structure. Subunits of NMDAR and AMPAR have the similar membrane topology: three membrane-spanning domains (M1, M3, and M4), a hydrophobic hairpin domain (M2), an extracellular N-terminus, and an intracellular CT. The GluN2A and GluN2B CT are particularly long, which harbor most of protein-protein interactions and phosphorylation so far characterized [3,4]. GluA1-4 CT tails are much shorter than NMDAR GluN2A/B CT. However, they are sufficient to harbor dynamic protein-protein interactions and phosphorylation [3,4].

Both NMDARs and AMPARs are tyrosine-phosphorylated [10.11]. With regard to NMDARs, early pharmacological studies demonstrated a significant impact of nRTK inhibitors on NMDAR activity [10,11]. Further mapping studies discovered accurate tyrosine sites in

individual NMDAR subunits that are phosphorylated by nRTKs [12]. For instance, Src and Fyn induced detectable tyrosine phosphorylation in the GluN2A CT region [13]. Effective phosphorylation sites include Y842, Y1292, Y1325, and Y1387 [13,14]. GluN2B CT was also tyrosine-phosphorylated by Fyn and a cluster of tyrosine residues (Y1252, Y1336, and Y1472) were identified as actual phospho-accepting sites [15]. Among these tyrosine residues, Y1472 seems to be a major site at which robust phosphorylation could be detected *in vitro* and in neurons using a phospho- and site-specific antibody [15]. Interestingly, unlike GluN2 subunits, GluN1 subunits are seemingly insensitive to nRTKs [12]. Tyrosine phosphorylation of AMPARs has also been investigated. The nRTK member Lyn seems to be an important kinase to catalyze tyrosine phosphorylation of AMPARs. This kinase interacts with the AMPAR GluA2 subunit [16], which promotes the kinase to phosphorylate GluA2 at Y876 [17]. Further studies reveal that Y876 phosphorylation is specific to the Src family of nRTKs (Lyn, Src, and Fyn), while the Fak family of nRTKs (Fak and Pyk2) did not phosphorylate this site [17].

Tyrosine phosphorylation has functional consequences. Tyrosine phosphorylation of NMDARs controls overall cellular expression of the receptor or confined expression of the receptor in a specific subcellular compartment. Fyn-mediated Y1336 phosphorylation regulated total cellular expression of NMDARs by modulating the calpain-dependent cleavage of GluN2B [18]. GluN2B Y1472 and Y1336 phosphorylation site-selectively enriched GluN2B/NMDAR abundance in synaptic and extrasynaptic compartments, respectively [19]. The regulated expression of the receptor is thought to translate to the modulation of receptor efficacy. In support of this notion, GluN2A Y1325 phosphorylation by Src potentiated the efficacy of NMDARs [14]. Furthermore, Src and Fyn induced an increase in GluN2A and GluN2B tyrosine phosphorylation, respectively, to potentiate NMDAR currents [20]. Src linked pituitary adenylate cyclase activating peptide 1 receptors to GluN2A, while Fyn connected dopamine D1 receptors to GluN2B, both of which led to tyrosine phosphorylation of GluN2A/B and augmentation of NMDARs. Like NMDARs, AMPARs are regulated by tyrosine phosphorylation for their expression and function. Y876 is a major phosphorylation site in GluA2 AMPARs. This site overlaps with the region of 880-SVKI-883, a binding site for PDZ domain-containing scaffold proteins, such as glutamate receptor interacting proteins 1 and 2 (GRIP1/2) which stabilize surface expression of the receptors. Thus, an increase in Y876 phosphorylation could disrupt the GluA2-GRIP1/2 association, which accelerated GluA2 endocytosis and reduced the level of surface AMPARs [17].

In addition to glutamate receptors, two common forms of synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), are modulated by nRTKs. Early studies showed that tyrosine kinase inhibitors blocked the induction of hippocampal LTP and cerebellar LTD [21,22]. Tyrosine kinase-deficient mice showed the lack of hippocampal LTP, learning, and memory [23,24]. Src was able to lower the LTP threshold, while Fyn was able to enhance LTD [20]. In GluN2B NMDARs, Y1472 phosphorylation was enhanced during the induction of LTP in hippocampal neurons [15]. In GluA2 AMPARs, insulin and low-frequency stimulation (LFS) enhanced tyrosine phosphorylation [25]. Such enhanced tyrosine phosphorylation was necessary for insulin- and LFS-induced AMPAR endocytosis

and LTD [25]. A peptide that competitively inhibited tyrosine phosphorylation of GluA2 CT blocked LTD induced by different stimulation paradigms [26]. Of note, in an mGluR1/5 agonist-induced LTD (i.e., DHPG-LTD which is believed to be induced via a different mechanism as compared to NMDA-LTD), tyrosine phosphorylation of GluA2 was reduced as a result of activated protein tyrosine phosphatases [27,28]. This dephosphorylation is crucial for AMPAR internalization and DHPG-LTD, although not for NMDA-LTD, in the hippocampus. Together, the nRTK members enriched at synaptic sites act as a point of convergence for many signaling pathways and coordinately regulate synaptic plasticity.

Tyrosine phosphorylation of group I mGluRs by nRTKs

Compared to extensive investigations of iGluRs, mGluRs have been less thoroughly studied for potential tyrosine phosphorylation and regulation. Among mGluR subtypes, group I mGluRs (mGluR1/5) seem to have potential to be substrates of nRTKs. Group I mGluRs are typical membrane-bound GPCRs. These receptors possess seven transmembrane helices, giving rise to multiple intracellular domains: three intracellular loops and an intracellular CT. Among these intracellular domains, CT tails are particularly noteworthy. They are relatively large and accommodate most protein-protein interactions so far discovered [29,30]. In addition, the mGluR1/5 CT region is the only intracellular domain containing tyrosine residues. Thus, tyrosine phosphorylation, if there is any, are thought to occur in this domain.

The first evidence supporting that mGluR5 might be a tyrosine-phosphorylated protein came from an early study, in which mGluR5 immunopurified from the rat brain exhibited abundant phosphotyrosine signals [31]. A protein phosphatase inhibitor (pervanadate) elevated the amount of tyrosine-phosphorylated mGluR5, indicating the existence of an active phosphorylation and dephosphorylation cycle controlling the level of tyrosine phosphorylation of mGluR5 under normal conditions. Tyrosine phosphorylation of mGluR5 is also sensitive to changing synaptic input. There is evidence showing that mGluR5 tyrosine phosphorylation is upregulated by NMDAR signals. In rat brain tissue, NMDA treatment enhanced mGluR5 tyrosine phosphorylation [31]. This agonist-induced mGluR5 tyrosine phosphorylation may constitute a molecular basis for activity-dependent crosstalk between NMDARs and mGluR5. The specific nRTK member(s) affecting mGluR5 and accurate tyrosine phosphorylation site(s) in mGluR5 are unknown at present. A simple sequence analysis revealed a total of four tyrosine residues in the distal mGluR5 CT. Thus, robust tyrosine phosphorylation is believed to occur among these sites. Functional roles of tyrosine phosphorylation of mGluR5 remain largely unknown. It appears that mGluR5 tyrosine phosphorylation has a minimal impact on the conventional mGluR5 signaling pathway given that pervanadate treatment unaltered mGluR5-stimualted and Gαq-coupled phosphoinositide hydrolysis [31]. However, tyrosine phosphorylation may contribute to 1) receptor desensitization usually occurred in response to repeated or prolonged agonist stimulation, or 2) additional receptor signaling through G protein-independent pathways. These activities usually involve use-dependent trafficking and anchoring of receptors.

Tyrosine phosphorylation of glutamate receptors in major depressive disorder

Major depressive disorder is a common form of mood disorders. An array of brain sites and circuits are implicated in this mental illness, central among which include the prefrontal cortex and hippocampus [32]. In addition to the well-documented monoamine mechanism, increasing data support the contribution of non-monoamine-based systems, such as glutamatergic transmission, to major depression and antidepressant activity [33-36]. Magnetic resonance spectroscopy showed an altered glutamate level in the cortex of depressed subjects [34], indicating a model of excessive glutamate excitation in depression. Consistent with this, NMDAR blockers antagonized depressant-like activity [33,34]. Similarly, GluN2A knockout mice showed anxiolytic- and antidepressant-like profiles [37]. Group I mGluRs are also implicated in the pathogenesis of depression [38]. A number of reports consistently showed that mGluR1 and especially mGluR5 antagonists produced antidepressant-like effects in various stress models [39-43]. Similarly, mGluR5 knockout mice displayed an antidepressant-like behavioral phenotype [42]. Apparently, both iGluRs and mGluRs are actively involved in depression and are useful targets for developing antidepressant agents.

Molecular mechanisms underlying the glutamate receptor participation in depression are poorly understood at present. As an effective way to modify glutamate receptor expression and function, tyrosine phosphorylation may play a role in processing glutamate receptor plasticity related to depression behavior. In fact, results from a recent study support this view. Mutation of Y1325 to phenylalanine (Y1325F) in the NMDAR GluN2A subunit prevented the phosphorylation at this site in transgenic mice *in vivo* [44]. Meanwhile, Y1325F mice showed antidepressant-like behavior in the tail suspension test and forced swim test. Since Y1325 phosphorylation mediates Src-induced potentiation of NMDARs, GluN2A Y1325 phosphorylation appears to be a critical element in potentiating NMDARs and promoting depression-like behavior. In addition to GluN2A, GluN2B is sensitive to stress that causes depression. Forced swim induced tyrosine phosphorylation of GluN2B [45], which may contribute to a metabasis leading to NMDAR plasticity and depression behavior. Of note, anxiety-like behavior that is usually associated with depression-like behavior seems to involve a different NMDAR response. Anxiety-producing stress induced dephosphorylation of GluN2B Y1472 [46]. Y1472F mutation increased corticotropin-releasing factor expression in the amygdala and enhanced anxiety-like behavior in mutant mice [46].

Whether tyrosine phosphorylation of mGluRs is sensitive and contributes to major depression has not been explored and thus remains as an interesting topic in future studies. Given the importance of glutamatergic transmission in this particular mood disorder, mGluRs are believed to play a pivotal role. It is likely that chronic stress induces long-term remodeling of mGluRs in discrete brain regions via a mechanism involving tyrosine phosphorylation, which then contributes to expression of depression-like behavior.

Conclusion

This review summarizes tyrosine-specific phosphorylation of glutamate receptors. In general, nRTKs such as Src and Fyn that are enriched at excitatory synapses can readily phosphorylate iGluRs and mGluRs. Robust phosphorylation usually occurs at a specific tyrosine or a cluster of tyrosine residues in CT tails of NMDAR and AMPAR subunits. The CT region of mGluR5 also contains tyrosine site(s) subjected to the phosphorylation by nRTKs. Both basic and phasic phosphorylation has a great impact on expression and function of modified receptors. Through phosphorylating glutamate receptors at tyrosine sites, nRTKs are implicated in the pathophysiology of major depression disorders. It is evident that the investigation of tyrosine phosphorylation of glutamate receptors and its functional roles is still at its infant stage. Future studies will aim to identify new tyrosine phosphorylation sites in intracellular domains of glutamate receptors, especially mGluRs. In addition, phosphorylation occurs at not only tyrosine, but also other amino acids, i.e., serine and threonine. Moreover, phosphorylation could occur together with other posttranslational modifications, including ubiquitination, palmitoylation, and sumoylation. All these modifications are an enzymatic process, which are inducible, regulatable, and reversible [3]. Thus, dynamic crosstalk may take place among phosphorylation at different sites and among different posttranslational modifications. It will be intriguing to investigate whether and how these crosstalk pathways act in concert to regulate glutamate receptors. Finally, clinical relevance of glutamate receptor tyrosine phosphorylation is poorly understood. It is thought that tyrosine phosphorylation of glutamate receptors may undergo drastic adaptations in mood disorders such as depression, which contributes to the pathophysiology and symptomology of depression. A useful tool is an animal model in which loss-of-function mutation (tyrosine to phenylalanine mutation) is achieved. Therefore, the role of a specific tyrosine phosphorylation site in the regulation of a receptor and in the pathogeneses of a disease can be investigated *in vivo*.

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