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**ARTICLE** *in* MOLECULAR NEUROBIOLOGY · NOVEMBER 2014

Impact Factor: 5.14 · DOI: 10.1007/s12035-014-9009-x · Source: PubMed



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# Modulation of the NMDA Receptor Through Secreted Soluble Factors

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Received: 30 July 2014 / Accepted: 14 November 2014


**Abstract** Synaptic activity is a critical determinant in the formation and development of excitatory synapses in the central nervous system (CNS). The excitatory current is produced and regulated by several ionotropic receptors, including those that respond to glutamate. These channels are in turn regulated through several secreted factors that function as synaptic organizers. Specifically, Wnt, brain-derived neurotrophic factor (BDNF), fibroblast growth factor (FGF), and transforming growth factor (TGF) particularly regulate the *N*-methyl-D-aspartate receptor (NMDAR) glutamatergic channel. These factors likely regulate early embryonic development and directly control key proteins in the function of important glutamatergic channels. Here, we review the secreted molecules that participate in synaptic organization and discuss the cell signaling behind of this fine regulation. Additionally, we discuss how these factors are dysregulated in some neuropathologies associated with glutamatergic synaptic transmission in the CNS.

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Published online: 29 November 2014

**Keywords** NMDA receptor · Soluble factors · Glutamate · Synapse · Neurotrophic · Neuroregulation

## Introduction

The obligatory balance between synaptic plasticity and excitotoxicity, in which the *N*-methyl-D-aspartate receptor (NMDAR) is a major player, is essential for the precise regulation of the dynamic distribution of this receptor. The receptor distribution is controlled not only through the internal clock (i.e., the GluN2A/GluN2B shift), but also through external signals that participate in synaptic formation and fine-tuned control beyond the amino acid sequence signals and structural domains of proteins attached to the presynaptic or postsynaptic neuronal cell. The final destination and changes associated with the dynamic synaptic structure are highly influenced through external components, particularly soluble molecules, secreted from the neuron itself or other cells [1, 2].

Synaptic components could be modulated through either direct interactions with receptors or signaling cascades in cross talk with mechanisms associated with synaptic remodeling and plasticity [3, 4].

In this review, we focus on synaptic function and the major protein families, including Wnt, brain-derived neurotrophic factor (BDNF), transforming growth factor (TGF)-β, and fibroblast growth factors (FGFs), which specifically modulate glutamatergic transmission and, more specifically, NMDAR synaptic transmission in the CNS.

## Biology of the *N*-Methyl-D-Aspartate Receptors

In the mammalian brain, fast excitatory synaptic transmission is mainly mediated through glutamate and its ionotropic receptors α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic

acid (AMPA) and NMDA. Unique properties, including $Ca^{2+}$ permeability, the voltage-dependent sensitivity to $Mg^{2+}$ and modulation through glycine, mediate the critical subunit-dependent role for NMDARs in brain development, neuropathology, and synaptic plasticity [5–9]. In addition, NMDARs play a structural role at the synapse through the recruitment of scaffolding and signaling complexes [10, 11]. The number, properties, and subunit composition of synaptic NMDARs are critical for proper synaptic functioning and the integrity of the synapse, and these factors must be well controlled to regulate $Ca^{2+}$ influx and different signaling cascades associated with the activation of this receptor.

The dysregulation of $Ca^{2+}$ influx through NMDAR not only contributes to neuronal death during acute damage, such as traumatic brain injury and ischemia, but also contributes to neuronal cell loss in several neurodegenerative diseases, such as Alzheimer's and Huntington's diseases [12–14].

Structurally, NMDAR is a heterotetrameric channel pore formed by the obligatory subunit GluN1 and either GluN2 or GluN3 subunits. These subunits contain several variants: unique GluN1 subunits with eight splice variants, four GluN2 subunits (GluN2A–D), and two GluN3 subunits [15]. Each subunit has an extracellular N-terminus, three transmembrane segments, a reentrant loop that forms the channel pore, and an intracellular C-terminus. Functional NMDARs, in the forebrain of the central nervous system (CNS), primarily comprise two GluN1 subunits and two GluN2/3 subunits [15]. Glutamate binds the GluN2 subunit, while glycine, a co-agonist, binds the GluN1 subunit. The domain for $Mg^{2+}$ blockade and $Ca^{2+}$ permeability is in the pore formed by the internal loop [15]. Although GluN1 subunits are critical for the formation of a functional NMDAR, GluN2 subunits confer specific and key biophysical and pharmacological properties, including sensitivity to polyamines, protons, and $Zn^{2+}$ ions [16]; affinity for glutamate; modulation through glycine; specific $Ca^{2+}$ permeability; and differential channel kinetics, including open probability and deactivation time [17] (Fig. 1a). Additionally, GluN2 subunits confer specific properties for the trafficking and delivery of NMDAR to the plasma membrane and synaptic compartment [15, 18]. Recently, crystal structure of intact heterotetrameric GluN1-GluN2B NMDAR ion channel at 4 Å was described [19], and also crystal structure of GluN1-GluN2B NMDAR with the allosteric inhibitor, Ro25-6981, partial agonists, and the ion channel blocker, MK-801, was published [20]. Both manuscripts help to understand the functional differences with AMPA receptor structure defining subunit interfaces and structural basis for allosteric inactivation providing a molecular blueprinting for design of therapeutic compounds [19, 20].

In several brain structures, including the brain stem, hippocampus, and neocortex, the ratio of GluN2A/2B increases during early postnatal development [21]. For example, in the hippocampus, the selective GluN2B inhibitor, ifenprodil,

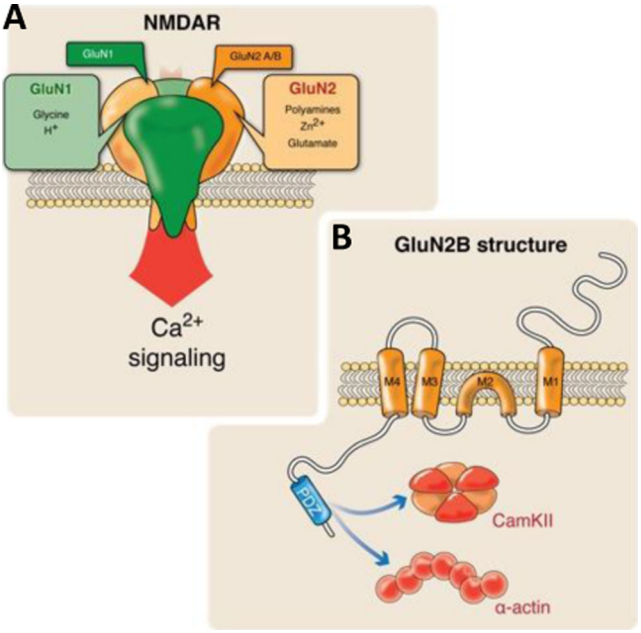


**Fig. 1** Schematic of the general structure of the NMDA receptor. **a** The tetrameric structure of the NMDA receptor with two GluN1 and two GluN2A/B subunits, indicating $Ca^{2+}$ signaling. The regulation of the receptor includes the effect of polyamines, glycine, $H^+$, $Zn^{2+}$, D-serine, and glutamate. **b** The structural domains of the GluN2B subunit of the NMDA receptor, showing a long C-terminus containing a PDZ domain for interactions with several postsynaptic proteins, including CamKII and α-actin

shows an age-dependent decrease in the blockade of NMDAR in rats between the ages of P1 and young adult [22]. Changes in the GluN2A/2B ratio can be estimated after measuring messenger RNA (mRNA) [23, 24] or protein [25] levels. Differences in the biophysical characteristics and structural properties of GluN2A or GluN2B confer physiological differences to the synapses containing these subunits. For long-term potentiation (LTP), the structural role of GluN2B-containing receptors is more critical than the role of the channels formed from these receptor subunits. LTP can still be induced when the GluN2B subunits are pharmacologically inhibited, but this induction is prevented when GluN2B expression is suppressed [26]. This structural role has been associated with the C-terminus of GluN2B (Fig. 1b). Therefore, wild-type GluN2A does not restore LTP in the absence of GluN2B (GluN2B RNAi), but replacing the C-terminus of the GluN2A subunit with the C-terminus of GluN2B restored LTP, suggesting that the C-terminus is critical [26]. Previous studies have shown that the CaMKII-binding domain in the C-terminus of GluN2B plays an important role in LTP induction [10] and the replacing synaptic GluN2B with GluN2A reduces synaptic plasticity. The switching of GluN2B with GluN2A also occurs after sensory experiences [25, 27], learning [28], and during development [23, 29]. However, changes in the biophysical properties of the synaptic NMDARs have not been associated with reduced

synaptic plasticity [30, 31]. Moreover, modifying the CamKII-binding domain of the GluN2B subunit reduces LTP [10].

The modulation of the GluN2A/2B ratio is not only associated with activity-dependent forms of synaptic plasticity, such as LTP. Indeed, the switch between GluN2 subunits implicates structural changes associated with different events, including synaptogenesis and synaptic pruning. Increasing GluN2A expression decreases the number of synapses, and although increasing the expression of GluN2B does not affect the number of spines, GluN2B increases both filopodia and spine motility, thereby inducing the addition and retractions of spines [32]. The effects on spine structure reflect the different roles of each C-terminal subunit during synapse formation and stabilization. The structural role of the C-terminus of NMDAR is not confined to the GluN2 subunits. Indeed, non-ionotropic NMDAR-dependent signaling through specific GluN1 C-terminal splice isoforms regulates the long-term stability and density of dendritic spines and the number of excitatory synapses [11]. The knockdown of the GluN1 subunit (essential subunit for NMDAR assembly) increased the motility of dendritic spines and the number of transient protrusions but decreased the spine density. These events have been associated with the C-terminal PDZ binding domain-dependent physical loss of NMDARs, as these effects are not observed in the presence of the pharmacological blockade of NMDARs [11].

Changes in F-actin regulate dendritic spine morphology through the regulation of postsynaptic proteins, such as NMDARs, AMPARs, and CaMKIIa, and postsynaptic density (PSD) scaffolds, including GKAP, Shank, and Homer [33–35]. Specifically, the C-terminus of the GluN2B and GluN1 subunits directly binds to α-actinin [36] (Fig. 1b). The CA3-targeted GluN2B-knock-out (KO) mice, with ablated GluN2B expression, reduced GluN1 expression and no effect on GluN2A, which shows a significant decrease in F-actin in the synaptosomal fraction [37].

In CA3-GluN2B-KO mice, the F-actin/G-actin ratio is reduced, affecting the formation of the postsynaptic complex and the formation and maintenance of dendritic spines [37] (Fig. 2).

The presence of specific GluN2 subunits in different domains suggests physiological and pathological roles for these proteins. The predominant GluN2 subunits in the mammalian forebrain, 2A and 2B, also control the trafficking of NMDARs based on subunit-specific rules, whereby the GluN2A subunits are more abundant in synaptic regions, while GluN2B is present in both synaptic and extrasynaptic domains. GluN2B-containing receptors have faster rates of diffusion than GluN2A-containing receptors, which contributes to the enrichment of GluN2A at mature synaptic sites [6]. Thus, GluN2B-containing receptors are inserted into synapses in an activity-independent or constitutive manner. In contrast,

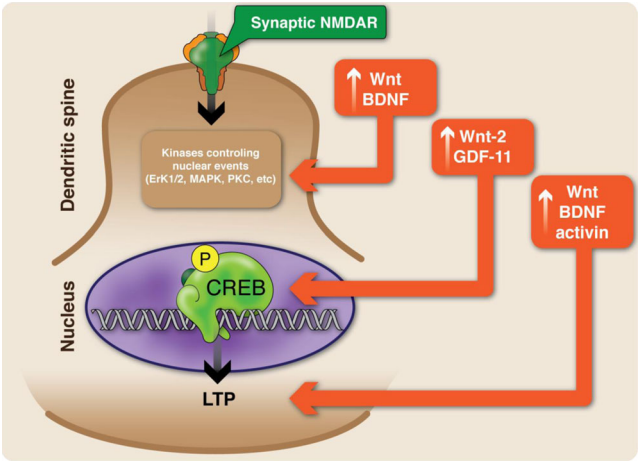


**Fig. 2** Effects of several soluble factors on the cellular pathways controlled through NMDA receptor activation. The targets include the receptors and downstream kinases, such as Erk1/2, MAPK, and PKC, for the regulation of CREB phosphorylation to control LTP. Wnt proteins, BDNF, and other factors function at different levels

the incorporation of GluN2A-containing receptors requires synaptic activity, and these receptors accumulate intracellularly when activity is blocked [38].

Alterations in the composition and distribution of NMDAR subunits modulates the amount of $Ca^{2+}$ influx into neurons, determining the ionic balance needed to maintain healthy conditions for the correct function of neuronal circuits, with several forms of regulation, including phosphorylation (Tables 1 and 2). The regulation of the composition and distribution of NMDAR is not only mediated through intracellular and intrinsic signaling, as these events are also regulated through external molecules not necessarily associated with electrical activity or housekeeping regulation. Indeed, these soluble factors are released in autocrine and paracrine forms, providing an additional level of control in the intricate regulation of the composition and function of postsynaptic components.

## Wnt

Wnt ligands are secreted glycoproteins that play a key role in neuronal development and connectivity [39–41], the regulation of axon guidance and remodeling [42], dendrite development [43], synapse formation [44–46], and synaptic plasticity [47–49], and some of these effects can be mediated through NMDAR. Wnt activity through the binding of Frizzled (Fz) subsequently triggers different downstream pathways [50], including the canonical Wnt/β-catenin control of gene transcription and the regulation of cytosolic microtubule dynamics, a non-canonical pathway that activates Rho GTPases and c-Jun N-terminal kinase (JNK) that induces changes in the cytoskeleton, and a non-canonical Wnt/$Ca^{2+}$ pathway that increases the intracellular $Ca^{2+}$ and the activation of CaMKII

**Table 1** Highlight structure/modification (phosphorylation) of NMDA receptor subunits under different enzymes

| Subunit | Structure/modification | Regulation by | Property/event affected | Reference |
|---|---|---|---|---|
| GluN1 | Phosphorylation, S890 and S896 | PKC | Receptor clustering | [112, 113] |
| | Phosphorylation, S897 | PKA | Surface expression and calcium permeation | [112, 114] |
| GluN2A | Phosphorylation, S900 and S929 | PKA | Desensitization | [115, 116] |
| | Phosphorylation, S1232 | Cdk5 | Increase NMDAR activity | [117] |
| | Phosphorylation, S1291, S1312, and S1416 | PKC | Increase GluN2A containing receptors, decrease affinity by CaMKII | [118–120] |
| | Phosphorylation, Y1292, Y1325, and Y1387 | Src | Potentiation of NMDAR currents | [121, 122] |
| GluN2B | Phosphorylation in PDZ-binding domain, S1480 | Casein kinase 2 | Diffusion in the membrane | [123] |
| | Phosphorylation, S1303 | CaMKII/PKC | Calcium entry | [124] |
| | Phosphorylation, S1323 | PKC | Activity potentiation | [125] |
| | Phosphorylation, Y1252, Y1336, and Y1472 | Fyn | Mediates endocytosis | [126] |
| | Phosphorylation, S1166 | PKA | Synaptic function and calcium permeation | [127, 114] |

and protein kinase C (PKC), two enzymes that control synaptic function and plasticity [51].

Little information is known about which the specific role of Wnt in NMDAR biology. First, Cappuccio et al. [52] showed that lithium, an inhibitor of glycogen synthase kinase (GSK)-3β, protects neurons against NMDA excitotoxicity. In this context, Wnt-5a also exhibits a protective role against the reduced expression of NMDAR and PSD-95 through Aβ oligomers [53]. Indeed, Wnt-5a occludes the Aβ-mediated synaptic depression of excitatory postsynaptic currents (EPSCs) and reduces PSD-95 clusters in neuronal cultures [54]. In retinal ganglion cells (RGC), Norrin, an Fzl4 ligand, prevents NMDA damage through the expression of several factors that increase the number of surviving RGC axons and decrease the apoptotic death of retinal neurons following NMDA-mediated damage. This effect is induced through Wnt/β-catenin [55, 56]. In addition, Wnt-7a, lithium (GSK-3β inhibitor), and MK801 (a NMDA blocker) showed protective roles in dystrophic networks, apoptosis, $Ca^{2+}$ increase, and the loss of mitochondrial membrane potential induced through Aβ-AChE complexes [57]. However, in terms of function, Wnt-7a has no effect on NMDAR-mediated synaptic transmission, whereas Wnt-5a, the non-canonical ligand, upregulates synaptic NMDAR currents, facilitating LTP. In addition, endogenous Wnt ligands maintain basal NMDAR synaptic transmission and adjust the threshold for synaptic potentiation. Therefore, Wnt ligands could modulate synaptic plasticity and brain function during later stages of development and in mature organisms [48] (Fig. 2). Other studies have shown that NMDA and Wnt signaling are impaired in the Traf2 and Nck-interacting kinase (TNiK) KO, which exhibits difficulties in spatial discrimination, glutamatergic signaling-dependent object location learning, and hyperlocomotor behavior [58]. Wnt ligands and the activation of NMDAR can also modify the NMDAR activity through the regulation of glutamate levels in osteoblastic cells. Wnt and NMDAR activation inhibits the activity of glutamine synthetase [36], thereby increasing the glutamate concentration through a decrease in the conversion of this compound to glutamine. This effect has been associated with the differentiation of osteoblasts, as GS activity declines during bone mineralization [59].

**Table 2** Soluble factor and target over signaling associated to glutamatergic transmission

| Soluble Factor | Target | Reference |
|---|---|---|
| Wnt | | |
| 5a | Upregulation of synaptic NMDA current | [48] |
| | Occlusion of Aβ-depression on EPSCs and decrease of PSD-95 cluster | [54] |
| 7a | No effect at postsynaptic level. Protective role in dystrophic neurons, $Ca^{2+}$ increase, and loss of mitochondrial membrane potential induced by Aβ-AChE complexes | [57] |
| 2 | It transcription is induced by CREB through NMDAR-$Ca^{2+}$ entry. Stimulates dendritic arborization | [66] |
| BDNF | NMDA receptor phosphorylation | [77] |
| | GluN1 phosphorylation | [78] |
| | GluN2B phosphorylation | [79] |
| | NMDA clustering induction | [84] |
| | NMDA channel open probability modulator | [85, 86] |
| FGF | Increases of mRNA of NMDA receptor | [93] |
| | Increase neuronal branching | [94] |
| | Participation in neurogenesis and plasticity including LTP | [95] |
| TGF | Increases of NMDA receptor level | [101] |
| | NMDA receptor phosphorylation inducing Ca2+ influx | [102] |
| | By GDF11 (TGF family protein) increases in CREB phosphorylation | [106] |

Other functions of the Wnt pathway include the enhancement of gene expression through the downstream effector β-catenin. This enhanced gene expression can be activity dependent, as the activation of calpain through NMDA induces β-catenin cleavage at the N-terminus, generating stable truncated forms that accumulate in the nucleus and induce the Tcf/Lef-dependent transcription of genes, such as Fosl1 [60]. Calpain also cleaves N-cadherin and subsequently interacts with β-catenin to modulate the expression of this gene [61]. Following NMDAR activation, the expression of several proteins, such as ADAM10 and β-catenin, increases through both the Wnt pathway and ERK kinase [62]. Indeed, D-serine, a co-activator of NMDAR, apparently triggers the upregulation of Wnt signaling genes, such as the gene encoding the catalytic beta subunit of cAMP-dependent protein kinase [63]. Wnt/β-catenin has also been implicated in drug-induced changes in transporter expression, and in the epileptic brain, glutamate stimulates the endothelial form of NMDAR, inducing the expression of P-glycoprotein, a protein involved in blood-brain barrier permeability, which affects several central nervous diseases [64]. In addition, the activation of Wnt signaling in the spinal cord during neuropathic pain stimulates the production of the GluN2B subunit of NMDAR and the generation of $Ca^{2+}$ signals through the β-catenin pathway [65]. In turn, neuronal activity mediated through $Ca^{2+}$ entry via NMDAR also enhances the CREB-dependent synthesis and secretion of Wnt-2 (Fig. 2). Wnt-2 couples neuronal activity with dendritic arborization, as this protein stimulates dendritic arborization [66] (Fig. 3). Moreover, NMDA activation induces the rapid synthesis and secretion of Wnt-5a protein. NMDAR-regulated Wnt-5a synthesis does not require transcription and results from activity-dependent translation, as treatment with anisomycin, a translation inhibitor, suppresses this effect. NMDAR-dependent Wnt-5a synthesis depends on MAPK, but not mammalian target of rapamycin (mTOR), signaling, as MEK inhibitors impair this process, whereas rapamycin, the mTOR blocker, has no effect [67].

Previous evidence has also demonstrated that Wnt signaling through NMDAR is involved in dendritic refinement and stimulates dendrite spine morphogenesis. Indeed, dendritic refinement potentially reflects NMDAR stimulation, and this activity triggers Wnt signaling, which plays a proretraction role in dendritic arbors [68]. Wnt-5a, expressed early during development, increases the amplitude of NMDAR spontaneous miniature currents and intracellular $Ca^{2+}$ in dendritic processes, stimulating spine morphogenesis, inducing the de novo formation and increasing the size of spines. This phenomenon is reversed through scavengers of Wnt [69]. Altogether, these effects suggest that the activation of Wnt signaling through NMDAR stimulation is associated with activity-coupled neurogenesis, neuronal development [70, 71], synapse formation [48], and learning and memory processes [58]. The mechanism underlying the Wnt-mediated

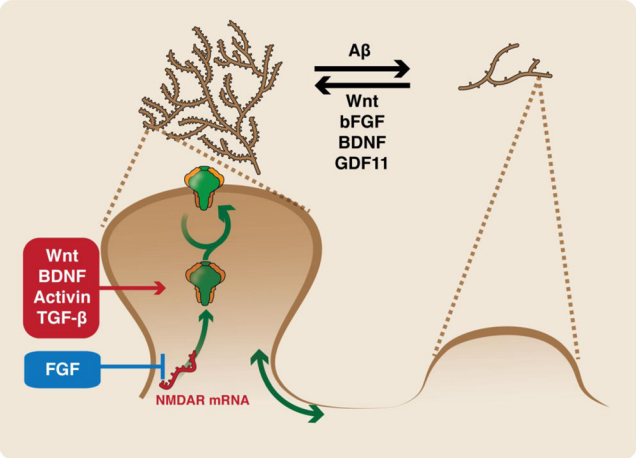


**Fig. 3** Modulation of NMDA receptor in the synapse and the effects on synaptic spines and branching. The NMDA receptor is delivered to the synapse under the regulation of several soluble factors; this regulation not only affects protein trafficking, but also regulates NMDA receptor mRNA levels (through FGF). Other soluble factors, such as Wnt, bFGF, BDNF, and GDF11, play active roles in synaptic branching and spine plasticity with opposite effects, such as deleterious events associated with Aβ

regulation of NMDA receptor dynamics involves an intermediary role for nitric oxide (NO) [72]. Indeed, Wnt-5a increases the GluN2B subunit of the NMDA receptor on the hippocampal neuronal cell surface, and this increase is mediated through NO production [72].

## Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophin family, which includes neurotrophin-3 (NT-3), NT-4–5, and nerve growth factor (NGF) [73, 74]. BDNF not only participates in the regulation of cell survival, development, and differentiation but also regulates synaptic transmission and plasticity [75]. The regulatory function of BDNF works at different levels. Herein, we discuss the specific regulation of NMDAR and the implications on synaptic function.

NMDAR is highly regulated, particularly through phosphorylation [76], and BDNF participates in this regulation [77]. Using hippocampal synaptoneurosomes (including presynaptic and postsynaptic elements) and isolated PSD, treatment with BDNF specifically enhances the phosphorylation of GluN1 NMDAR subunits [78]; however, no effect of NGF was observed at 5 min after exposure. In mature cortex and hippocampal PSD preparations, containing TrkB receptors, BDNF also enhances the phosphorylation of GluN2B NMDAR subunits [79]. Phosphorylation at tyrosine 1472 stimulates synaptic transmission and enhances the amplitude of synaptic currents through the enrichment of GluN2B on membrane surface of synaptic regions [80]. Fyn kinase

mediates the phosphorylation of GluN2B subunits at tyrosine 1472 [81], and BDNF modulates Fyn activity through the TrkB receptor [82] (Figs. 2 and 3). In Fyn KO mice (Fyn −/−), the Fyn-mediated basal phosphorylation GluN2B was decreased 20 % compared with the wild-type control [82]. Moreover, in wild-type mice, BDNF increases GluN2B phosphorylation 1.9-fold, but this effect was not observed in KO mice (Fyn −/−) [82].

Electrophysiological measurements of evoked currents in hippocampal culture neurons confirmed the importance of GluN2B subunits for BDNF function in glutamatergic transmission, and AP-5 (a NMDAR inhibitor) and ifenprodil (a specific GluN2B inhibitor) showed similar effects, partially inhibiting the BDNF effect on glutamatergic synaptic currents [83], suggesting that GluN2B inhibition plays an important role in this effect. In addition, BDNF induces NMDAR clustering during the maturation of hippocampal synapses in culture [84], and this mechanism is $GABA_A$ dependent; bicuculline abolishes this effect. Moreover, $GABA_A$ clustering is also necessary for TrkB-mediated and activity-dependent events [84]. These regulations have physiological consequences, including increased $Ca^{2+}$ concentration in response to NMDA treatment [77]. Cultured hippocampal neurons loaded with a $Ca^{2+}$ indicator (fura-2) showed an important response to NMDA treatment after incubation with BDNF [77]. The increased NMDAR functions could reflect modifications in the properties of this receptor, including open probability [85]. In hippocampal neurons, BDNF enhances responsiveness to the iontophoretic application of glutamate or NMDA, increasing the amplitude and the open probability [85], and these effects occur in response to BDNF exposition, but not with NGF or NT-3 treatments. The BDNF effect is selective for the NMDA receptor because neither AMPA nor acetylcholine responses are affected by BDNF [85]. Signaling for NMDAR modulation through BDNF also includes PKC pathways [86]. In rat spinal cord preparations, BDNF treatment increases the phosphorylation of GluN1 subunits, specifically at serine 897 [86]. This phosphorylation is mimicked by the PKC activator, phorbol myristate acetate (PMA), and is inhibited by the PKC inhibitor, chelerythrine [86] (Fig. 2a).

The Wnt-mediated regulation of BDNF adds another level of complexity. So far, in this manuscript, we have described a role for Wnt in the control of glutamatergic transmission and the roles for several effector proteins, including several kinases (PKC, CaMKII) and scaffold proteins (PSD-95), including calcium influx. However, β-catenin, the main effector of Wnt signaling activation, binds DNA in putative Tcf/Lef regions in the promoter and exons of the BDNF genes in humans and rodents [41]. Experimental confirmation in glial cells showed that BDNF is a direct target of the canonical Wnt pathway [87].

## Fibroblast Growth Factor

The fibroblast growth factor (FGF) family includes 22 members with four FGF receptors [88]. These ligands are polypeptides with diverse biological activities, including differentiation, cell proliferation, and migration [89–91].

Basic FGF (bFGF or FGF-2) is effective in suppressing the oxidative impairment of synaptic transporter functions through a mitochondria-dependent mechanism [92]. Several years ago, a role for bFGF in the regulation of NMDAR expression was proposed [93]. Indeed, a reduction in the levels of NMDAR mRNA was observed in bFGF-treated neurons, and this effect was specific, as the level of kainate/AMPA receptor mRNA did not change in the treated neurons [93]. Additionally, bFGF increases the outgrowth of axons and dendrites and might also increase the complexity (branching) of the neurites in embryonic hippocampal neurons [94] (Fig. 3).

Conditional KO mice for the FGFR1 gene were generated to determine the role for the FGF receptor in neurogenesis and synaptic plasticity in the dentate gyrus [95]. Deficits in neurogenesis in KO mice were accompanied by LTP and memory consolidation impairment [95]. In the presynaptic counterpart, FGF22 and the closely related FGF7 and FGF10 promote several aspects of presynaptic differentiation, playing a key role in synaptic differentiation [96]. This dual control of presynaptic and postsynaptic components through the same family of soluble factors plays a role in targeting diverse molecules to control synaptic organization.

## Transforming Growth Factor

Transforming growth factor-β (TGF-β) signaling controls several cellular processes, including cell proliferation, differentiation, apoptosis, and others cellular events, from flies to mammals [97]. The TGF-β family comprises TGF-β, activins, Nodal, bone morphogenic proteins (BMPs), growth and differentiation factors (GDFs), and anti-Mullerian hormone (AMH) [98].

In general, studies concerning the role of TGF-α or β in NMDAR modulation have involved excitotoxic models, focusing on the putative role for TGF-β in the toxicity mechanism. In a retina model of neuronal damage induced through the intravitreal injection of NMDA, the use of the inhibitors SB431542 and LY364947 to block TGF-β signaling prevented the progression of neuronal cell death [99]. Thus, TGF-α shows a protective effect against NMDA-induced toxicity [100]. In mixed neuron-glia cultures treated with TGF-α, the neuronal cell death induced through NMDA exposure was attenuated, showing a decrease in elevated intracellular $Ca^{2+}$ elicited, lactate dehydrogenase release, propidium iodide staining, and caspase-3 activation [100].

Additionally, the protein levels of NMDAR and AMPA were increased in transgenic mice expressing high levels of TGF-β1 (t64 mice) [101]. Specifically, in the hippocampus of 2-month-old transgenic mice, the levels of GluN1 and GluN2A/B were enhanced more than 2-fold [101].

Activin, a member of the TGF-β superfamily, induces NMDAR phosphorylation, thereby increasing $Ca^{2+}$ influx through these receptors [102]. After LTP, activin, GluN2 NMDAR subunits, and other proteins form a functional complex that increases the expression of activin [103]. Dominant negative activin receptor IB mice showed a reduced NMDA current response and LTP impairment [104] (Fig. 2).

Considering that CREB phosphorylation is located downstream of NMDA activation in a synaptic potentiation context, the modulation of CREB through TGF factors might be a putative target for NMDA synaptic activation. Experiments with heterochronic parabionts, in which the circulatory systems of young and aged animals are connected, indicate that the exposure of aged mice to young blood late in life rejuvenates synaptic plasticity and improves cognitive function [105]. Complementary studies have shown that this effect is partially regulated through GDF11, a member of the TGF family [106]. These data suggest that circulatory soluble factors are modulators of cognitive function (memory and learning tasks), associated with changes in the structural substrates of plasticity (dendritic spines dynamic) [105, 106] (Fig. 4).

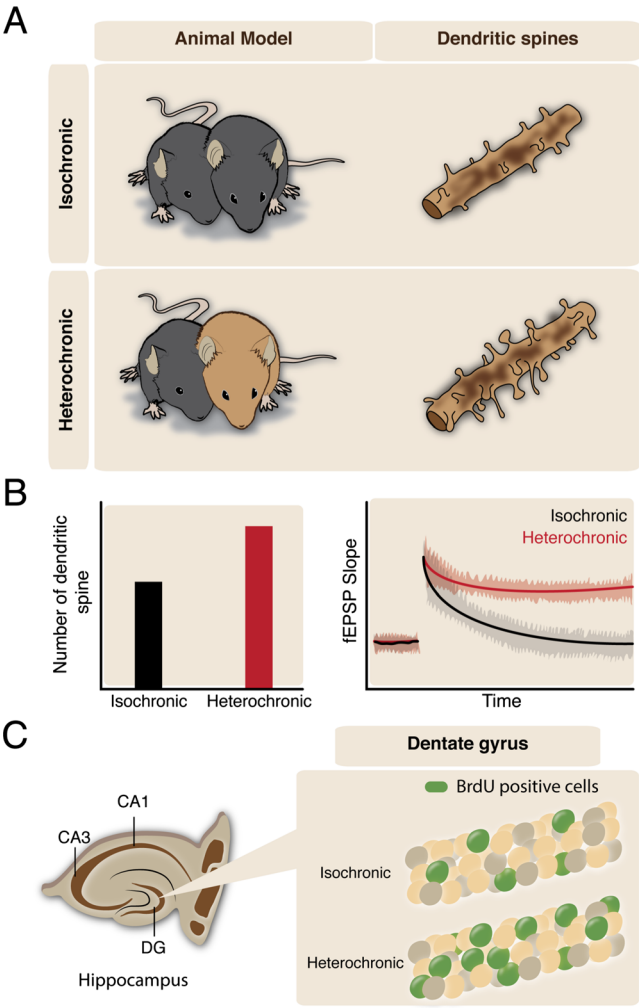


**Fig. 4** Heterochronic parabiosis improves several synaptic properties in older animals. **a** Exposure of aged mice to young blood late in life rejuvenates synaptic plasticity and improves cognitive function. **b** Increases in number of dendritic spines and enhanced LTP in heterochronic animal [105]. An increase in the number of new neurons is shown in the dentate gyrus, and a role for GDF11 is demonstrated [106]

## Conclusion and Projections

The roles for soluble secreted proteins, including Wnt, BDNF, FGF, and TGF, in biological events, such as embryonic development, cell proliferation, or axon guidance, have been described. However, in recent years, these factors have been implicated in the control of synaptic structure and function, including the regulation of components of the glutamatergic neurotransmission, such as NMDA receptors. Notably, these molecules participate in different control points for key functions. Through these proteins, the cell efficiently maintains the correct internal balance and responds to external stimuli.

Although the role for soluble factors from the Wnt family in embryonic development and cancer has been well characterized [107], the role for these proteins in preventing neuronal injuries, particularly those associated with Alzheimer's disease (AD), has only recently been described [41, 51, 108, 109].

The role for BDNF in cell survival and differentiation has been characterized for years, and its contribution to synaptic function has also been well described [74]. However, the coordinate action of BDNF together with other soluble factors is an unexplored avenue. FGF plays a role in proliferation and cell migration [110], and TGF controls several cellular processes, including cell proliferation, differentiation, and apoptosis, from flies to mammals [97]; although there are many examples of the individual roles for these factors, we cannot rule out the potential multitask properties of these soluble factors when working together. These factors share functional properties important for the maintenance of the cell, and the availability of these factors is important for acute and chronic changes during intracellular events, such as the insertion of the AMPA receptor during LTP. Multifunctionality ensures control of cell development through these molecules. We focused on Wnt, BDNF, FGF, and TGF because these molecules play active and specific roles for the control intracellular traffic and NMDAR function, suggesting a mechanism for the intervention of higher mental processes, such as learning and memory, under physiological or pathological conditions. Knowledge of the modifications that directly affect the receptor or receptor signaling is crucial to generate

specific tools for the external control (soluble molecules) of NMDAR function and synaptic plasticity. Current research efforts have focused on dissecting the connection map in the brain, the connectome, with huge progress [111]. Clearly, however, the next step will be to elucidate the mechanisms underlying the control of the interactions between neurons, including the autocrine and paracrine release of soluble factors, which are ultimately responsible for remodeling neuronal connections.

**Acknowledgments** This work was supported through grants from Fondecyt No. 11121206 to WC, Fondecyt No. 1120156 and the Basal Centre for Excellence in Science and Technology (Conicyt-PFB 12/2007) to NCI, and a postdoctoral fellowship from CONICYT Fondecyt Postdoctorado No. 3140355 to ERF. The authors would also like to thank Felipe Serrano for assistance with the artwork.

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