[Communicative & Integrative Biology 2:3, 261-264; May/June 2009]; ©2009 Landes Bioscience

Mini-Review

Neuregulin links dopaminergic and glutamatergic neurotransmission to control hippocampal synaptic plasticity

Jörg Neddens, Detlef Vullhorst, Daniel Paredes and Andres Buonanno*

Section on Molecular Neurobiology; Eunice Shriver Kennedy National Institute of Child Health and Human Development; National Institutes of Health; Bethesda, MD USA

Key words: neuregulin, ErbB receptor, D4 dopamine receptor, depotentiation

Neuregulin-1 (NRG-1) and its receptor ErbB4 are genetically associated with schizophrenia, a complex developmental disorder of high heritability but unknown etiology that has been proposed to result from deficits in functional connectivity and synaptic plasticity. Based on pharmacological evidence, imbalances in dopaminergic and glutamatergic transmission systems are believed to contribute to its pathophysiology, but genetic data supporting a causative role for either are sparse. Stimulation of NRG-1/ErbB4 signaling inhibits or reverts hippocampal long-term potentiation (LTP) at glutamatergic synapses between Schaeffer collateral afferents and CA1 pyramidal neurons (SC→CA1). We have recently demonstrated that NRG-1 regulates glutamatergic plasticity by rapidly increasing extracellular hippocampal dopamine levels and activation of D4 dopamine receptors.[7] These new findings position the NRG-1/ErbB4 signaling pathway at the crossroads between dopaminergic and glutamatergic neurotransmission and offer novel ways to consolidate genetic, functional and pharmacological data toward a better understanding of the etiological processes underlying schizophrenia, and the role of NRG-1 for normal synaptic function and plasticity. The currently available data suggest that hippocampal interneurons might play a crucial role in mediating NRG-1 induced depotentiation. This interpretation is in line with other evidence pointing towards an involvement of GABAergic cells in the etiology of schizophrenia.

Activation of NRG-1/ErbB4 Signaling Recruits a Dopaminergic Pathway to Regulate Early LTP at Glutamatergic CA1 Synapses

At SC→CA1 synapses, LTP is rapidly depotentiated by acute administration of NRG-1 during a labile period of ~30 min immediately following its induction.[1] In addition, NRG-1 can prevent the manifestation of LTP if applied prior to induction.[2,3] LTP can also be reversed by a brief train of electrical pulses at theta frequency (theta-pulse stimuli, TPS), and this TPS-mediated depotentiation is blocked by inhibitors of ErbB signaling, suggesting an involvement of the NRG/ErbB signaling pathway.[1]

Mechanistically, LTP depotentiation by NRG-1 represents the reversal of synaptic strength back to pre-LTP levels, and is mediated via the internalization of synaptic AMPA receptors containing the GluR1 subunit. Although previous work firmly established the inhibitory effects of NRG-1/ErbB signaling on LTP, the pathway leading from ErbB receptor activation to the removal of AMPA receptors selectively from potentiated synapses was unclear. On the other hand, mice heterozygous for NRG-1 display abnormal prepulse inhibition of the startle response, a behavioral abnormality that is also found in schizophrenic patients and that can be alleviated by treatment with the antipsychotic clozapine,[4] that primarily targets D2-type dopamine receptors.[5,6] This prompted us to investigate a possible involvement of the dopamine system in mediating NRG-1-induced depotentiation.

We found that perfusion of the dorsal hippocampus of behaving animals with NRG-1 causes a rapid (<2 min) and dramatic (~3-fold) increase in extracellular dopamine levels that lasted for about 15 minutes.[7] Conversely, pharmacological blockade of ErbB receptors produces a small but significant decrease of dopamine levels, consistent with a role for endogenous NRG-1 signaling in the regulation of dopamine (Fig. 1). We then investigated the involvement of dopamine receptors in LTP reversal and identified through the use of selective agonists and antagonists, as well as KO mice, the D4 dopamine receptor (D4R) as necessary and sufficient to trigger LTP depotentiation in response to NRG-1.[7] Moreover, TPS are not effective in attenuating LTP in D4R-knockout mice, further corroborating the notion that TPS and NRG-1 share a common pathway. Consistent with the idea that D4R could be an intermediate downstream target of NRG-1/ErbB4 signaling, we also showed that in cultured hippocampal neurons expressing D4R and treated to undergo a chemical form of LTP, D4R activation causes the internalization of surface GluR1-containing AMPA receptors, thus recapitulating the response in acute hippocampal slices.[7] Our slice recordings indicate that the depotentiating effects of NRG-1 and D4R agonists are local to CA1, since results were not different when CA3 was separated from CA1. This result is consistent with the distribution of dopamine fibers in hippocampus that innervate the subiculum and adjacent CA1 but not CA3 (reviewed in ref. 8), and with the presence of D4R mRNA in CA1/CA2.[7]

*Correspondence to: Andrés Buonanno; Section on Molecular Neurobiology, Building 35; Room 2C-1000; 35 Lincoln Drive; National Institutes of Health; Bethesda, MD 20892-3714 USA; Tel.: 301.496.017; Fax: 301.480.2707; Email: buonanno@helix.nih.gov

Submitted: 01/06/09; Accepted: 01/07/09

Previously published online as a *Communicative & Integrative Biology* E-publication: http://www.landesbioscience.com/journals/cib/article/7825

Complementary Roles of D1-Type and D4 Dopamine Receptors during LTP

Numerous studies have shown that D1/D5 receptors facilitate early-phase LTP[9] and have an important role in the consolidation of late-phase LTP in vitro[10,11] and in vivo.[12,13] In contrast, the role of D2-type receptors in LTP has been much less well defined. All dopamine receptors are G-protein coupled and modulate the production of cyclic AMP. Since D1-type receptors and D2-type receptors stimulate or inhibit adenylate cyclase activity, respectively, they may be expected to exert opposing effects on LTP. Interestingly, the D2/D3R antagonist domperidone has been shown to prevent late-phase LTP,[14,15] however, this effect required several hours to occur and thus likely reflects a different mechanism, since the specific activation of D4R in our study resulted in almost immediate depotentiation.[7] Our results show that local application of NRG-1 increases dopamine release in the hippocampus in vivo. Frey et al. showed that LTP-inducing 100 Hz tetanization of the SC→CA1 pathway temporarily increases the release of [^{14}C] from sections that were preloaded with [^{14}C]-dopamine.[14] However, while tetanus-elicited dopamine release could explain the stabilizing effects of dopamine signaling on late-phase LTP, it is unlikely to account for the rapid depotentiating effects of NRG-1 based on differences in timing and sign of action (pro-LTP vs. anti-LTP).

Location, Location, Location

Although conceptually the recruitment of the dopamine system by NRG-1 elegantly links ErbB4 signaling and glutamatergic plasticity, it is currently not clear where within the circuitry of the hippocampus the critical 'players' are located. It appears reasonable to assume that the D4R is expressed on CA1 principal neurons at or near SC→CA1 synapses in the stratum radiatum to locally trigger the reversal of LTP at potentiated sites (depotentiation by NRG-1 is homosynaptic; see ref. 1), based on our in vitro data showing that direct activation of D4R can trigger AMPA receptor internalization in transfected hippocampal neurons. On the other hand, D4R immunoreactivity in the primate hippocampus was shown to be high in some GABAergic interneurons,[16] suggesting that D4R activation could somehow reverse LTP by modulating GABAergic function. It is important to note, however, that D4R mRNA and protein levels are exceedingly low in the hippocampus, and its expression in pyramidal cells and/or interneurons is far from established.[16-18]

The known spatial distribution of some crucial elements might be helpful, however, in assembling a network model: First, ErbB4 is expressed in numerous GABAergic interneurons across all layers (see below). Second, glutamatergic SC→CA1 synapses are located in the stratum radiatum. Third, the dopaminergic innervation of the hippocampus is low and spatially restricted to the subiculum and adjacent CA1, especially in the dorsal part where electrophysiological recordings of LTP are typically performed; mesohippocampal dopaminergic fibers in CA1 terminate in stratum oriens close to the alveus or in stratum lacunosum moleculare, essentially excluding strata pyramidale and radiatum.[8,19] It is unclear if dopamine receptors located close to SC→CA1 synapses on pyramidal neurons could be directly activated by dopamine release from these terminals, even if considering the possibility of extrasynaptic volume transmission of dopamine as suggested in other brain areas such as the nucleus

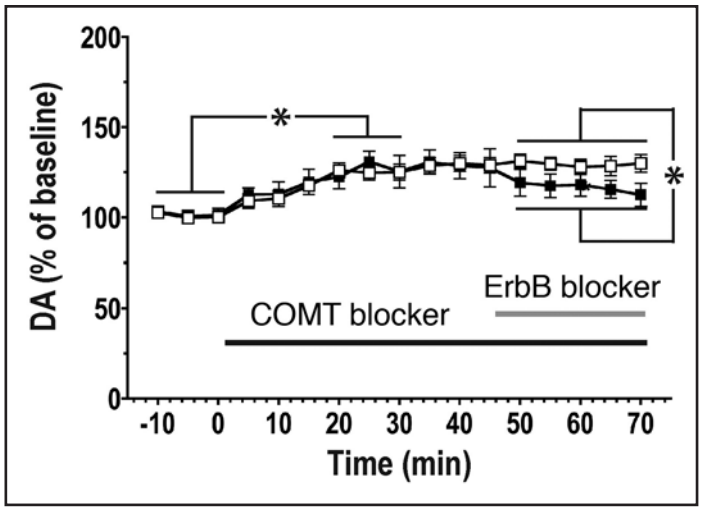

Figure 1. Blockade of endogenous NRG/ErbB signaling reduces dopamine release in the dorsal hippocampus of live behaving rats. Catechol-O-methyl transferase (COMT) activity was blocked with 100 nM Ro-41-0960 to prevent dopamine degradation and to analyze the effects of ErbB receptor inhibition (10 μM PD158780) on dopamine release. Dopamine levels rise steadily over 25 min following the onset of Ro-41-0960 infusion, consistent with the predominant role of enzymatic degradation in the clearance of extracellular dopamine in the hippocampus.[7] However, after additional infusion of the ErbB receptor inhibitor (solid squares), dopamine levels decrease significantly compared to controls that did not receive the blocker (open squares). Therefore, ErbB receptor activation is involved in the regulation of endogenous dopamine release. *$p < 0.05$ (2-way ANOVA). Data represent the mean ± SEM ($n = 5$ for both groups).

accumbens.[20] If dopamine receptors are present in the vicinity of dopaminergic fibers they could be located on distal portions of basal and apical pyramidal cell dendrites, on interneurons, or both. Finally, it is as of yet unclear whether hippocampal dopamine receptors are primarily postsynaptic or presynaptic, or whether cells co-express different types of dopamine receptors.

As for the location of ErbB4, direct receptor activation on dopamine terminals presents one conceivable way to promote release from afferents in the hippocampus. However, we did not find evidence for ErbB4 expression in dopamine neurons in the VTA or their afferent projections in the hippocampus. In contrast, the highest levels of ErbB4 mRNA and protein have consistently been observed in GABAergic interneurons, and these cells are good candidates to represent the proximate target for the effects of NRG-1 on glutamatergic plasticity in pyramidal cells. In agreement with this, NRG-1 has been shown to stimulate GABA release.[21]

Interestingly, hypofunction of GABAergic interneurons, in particular of cells that express parvalbumin (PV), has been suggested to contribute to the etiology of schizophrenia.[22-25] Basket and chandelier cells that provide powerful perisomatic inhibition control and time the population firing of principal glutamatergic neurons, thereby coordinating network activity. Acute activation of NRG-1/ErbB4 signaling strongly increases the power of kainate-induced gamma-oscillations in CA3 of the hippocampus, suggesting that it augments or synchronizes basket cell output.[26] However, it is not obvious how perisomatic inhibition of pyramidal cells could be linked to LTP reversal at their apical dendrites where SC→CA1 axons terminate. Of note, studies on the hippocampal distribution of ErbB4

unanimously show expression in numerous cells that are located in the apical strata radiatum and lacunosum moleculare, suggesting that ErbB4 expression in interneurons extends beyond perisomatic targeting cells (refs. 27 and 28; Neddens J and Buonanno A, unpublished). To understand if and how NRG-1/ErbB4 signaling regulates dopamine release via modulation of GABAergic function, it will be important to investigate in detail the extent to which ErbB4 is expressed in other interneuron subtypes that regulate and coordinate the flow of glutamatergic information through the hippocampal subfields, and to study mice with subtype-specific ablations of the receptor. Lastly, it will be imperative to identify the source of endogenous NRG that regulates plasticity at SC→CA1 synapses, and the conditions under which it triggers dopamine release (see below). Previous work suggests that NRG-1 can be released in an activity-dependent fashion, and that CA3 axons, perforant path fibers, and cholinergic afferents from the medial septum, are all potential sources.[29-31]

Implications for Schizophrenia

Glutamatergic, dopaminergic, GABAergic and cholinergic neurotransmitter systems have all been implicated in the etiology and pathophysiology of schizophrenia. Recently, a circuit-based framework of schizophrenia was proposed in which aberrant glutamatergic or cholinergic function reduces GABAergic control of principal neuron firing by parvalbumin-expressing basket and chandelier cells, thereby causing disinhibition of glutamatergic outflow from the hippocampus, increased neuronal activity in the VTA, and subsequent generation of a hyperdopaminergic state in the hippocampus.[32] Among the many genetic risk factors that have been implicated in this process, for the reasons mentioned above NRG-1 and ErbB4 seem uniquely positioned to link these neurotransmitter systems, in particular since ErbB4 is co-expressed in parvalbumin-positive interneurons.[25] However, whether NRG signaling causes dopamine release via a polysynaptic loop involving the VTA is presently unclear. While our dopamine measurements in live behaving animals are compatible with this idea, it should be noted that our electrophysiological experiments implicating D4R in NRG-mediated LTP reversal were performed in acute hippocampal slice preparations in which the VTA was removed,[7] thus favoring a local mechanism.

Historically, the NRG/ErbB signaling network is best known for its important role in the development and maturation of the peripheral and central nervous system, including the generation, migration and survival of inhibitory interneurons,[33-35] synaptic maturation,[36,37] and possibly the control of myelination of central axons[38,39] (but see ref. 40). In this way, NRG/ErbB signaling is involved in multiple neural processes potentially relevant to the etiology of schizophrenia, and alterations of which could conceivably increase the risk of developing the disorder later in adolescence.

It was recently shown that the schizophrenia-associated NRG-1 polymorphism SNP8NRG243177 correlates with impaired activation of the medial prefrontal and temporal cortex and affects IQ (refs. 41 and 42, but see ref. 43). However, it is still an open question whether hypo- or hyperactive NRG-1/ErbB4 signaling (or both) is associated with schizophrenia. Based on analyses of NRG-1 and ErbB4 mRNA levels in postmortem brains, increased expression of certain NRG-1 and ErbB4 isoforms was proposed in schizophrenic patients.[44,45] Moreover, ErbB4 signaling after stimulation with exogenous NRG-1 peptide is enhanced in synaptic membrane preparations from postmortem brains of affected individuals.[46] Taken together, these findings appear to favor a model in which hyperfunction of NRG-1/ErbB4 signaling contributes to schizophrenia. On the other hand, behavioral abnormalities that are consistent with some of the positive symptoms associated with schizophrenia have been observed in mice heterozygous for NRG-1 or ErbB4, suggesting that reduced NRG-1/ErbB4 signaling could trigger schizophrenia-like behavior.[4] Therefore, while there is ample data to suggest a link between NRG-1/ErbB4 signaling and the manifestation of schizophrenia-associated behavior, it is evident that we are still a long way from understanding how, and on what time scale, alterations in NRG-1/ErbB4 signaling contribute to the impairment of cognitive processes observed in schizophrenia. In particular, it is unclear whether the changes in NRG-1/ErbB4 function and expression observed in patients and postmortem brain samples represent direct effects or compensatory responses to some other primary perturbation. For the same reasons, caution needs to be exercised in trying to equate findings derived from the analysis of genetic animal models with those obtained from acute manipulations of the neuregulin/ErbB signaling network. We are confident, however, that our recent findings will encourage new studies in humans and mouse models to further explore the causative role NRG plays in the regulation of dopaminergic and glutaminergic transmission in the normal brain and under pathological conditions. It should also be mentioned that several recent studies have pointed towards a functional connection between NRG and the nicotinic α7 acetylcholine receptor (α7R),[47-49] the prospect of which is exciting since several lines of genetic and functional evidence point to an involvement of α7R with schizophrenia (reviewed in refs. 50 and 51).

Lastly, most studies have focused on the role of NRG-1 on synaptic function and plasticity. In this regard, it is important to emphasize, though, that the closely related NRG-2 is highly expressed in the adult brain and therefore conceivably serves as an important endogenous ligand for ErbB4, while NRG-1 expression is highest during neural development.[52] In contrast to NRG-1 mutant mice that die during early embryogenesis, NRG-2 deficient mice are viable and could therefore serve as a useful model to analyze the effects of impaired NRG/ErbB4 signaling on hippocampal function in the adult animal.[53]

Acknowledgements

The authors would like to acknowledge the Eunice Kennedy Shriver National Institute of Child Health and Human Development for their financial support.

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