NMDA Receptor Hypofunction, Parvalbumin-Positive Neurons, and Cortical Gamma Oscillations in Schizophrenia

Guillermo Gonzalez-Burgos[*] **and David A. Lewis**

Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh School of Medicine, W1651 Biomedical Science Tower, Pittsburgh, PA 15213

*To whom correspondence should be addressed; tel: 412-624-3934, fax: 412-624-9910, e-mail: gburgos@pitt.edu

Gamma oscillations appear to be dependent on inhibitory neurotransmission from parvalbumin (PV)-containing gamma-amino butyric acid neurons. Thus, the abnormalities in PV neurons found in schizophrenia may underlie the deficits of gamma-band synchrony in the illness. Because gamma-band synchrony is thought to be crucial for cognition, cognitive deficits in schizophrenia may reflect PV neuron dysfunction in cortical neural circuits. Interestingly, it has been suggested that PV alterations in schizophrenia are the consequence of a hypofunction of signaling through N-methyl-D-aspartate (NMDA) receptors (NMDARs). Here, we review recent findings that address the question of how NMDAR hypofunction might produce deficits of PV neuron–mediated inhibition in schizophrenia. We conclude that while dysregulation of NMDARs may play an important role in the pathophysiology of schizophrenia, additional research is required to determine the particular cell type(s) that mediate dysfunctional NMDAR signaling in the illness.

Key words: glutamate/GABA/inhibition

Introduction

Cognitive deficits, the major determinant of long-term functional outcome for schizophrenia patients,[1] reflect dysfunction of neural circuits in different cortical regions.[2] Because the neural substrate for cognitive function is thought to involve synchronization of neural activity at gamma-band frequency, abnormalities in cortical gamma oscillations may contribute to the cognitive deficits in schizophrenia.[1]

Gamma oscillations in cortical circuits appear to be dependent on inhibitory neurotransmission from the parvalbumin (PV)-containing subclass of gamma-amino butyric acid (GABA) neurons.[3,4] Thus, the abnormalities in molecular markers of PV neurons in schizophrenia[5] suggest that alterations of PV neuron–mediated inhibition may play a critical role in the deficits of gamma-band synchrony in the illness.

The dysfunction of PV neurons in schizophrenia has been suggested to be a consequence of a hypofunction of signaling through N-methyl-D-aspartate (NMDA) receptors (NMDARs) (for a recent review, see Nakazawa et al[6]). Although schizophrenia involves alterations in other interneuron subtypes and in oscillations of other frequencies,[7] this review is focused on how NMDAR hypofunction may produce deficits of PV neuron–mediated inhibition that could lead to the impairments of gamma oscillations that are correlated with cognitive dysfunction in schizophrenia.[1]

Specifically, we review: (1) studies in human subjects supporting the idea of NMDAR hypofunction in schizophrenia; (2) recent evidence supporting the role of PV neurons in gamma rhythm production; (3) circuit models of inhibition-based gamma oscillations; (4) the distinctive properties of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and NMDAR-mediated synaptic responses and their contributions to excitation of PV neurons; and (5) studies testing the effects of NMDAR antagonism on gamma oscillations. We conclude with a discussion of alternative scenarios regarding the role of NMDAR hypofunction and gamma oscillations in schizophrenia.

NMDAR Hypofunction Hypothesis of Schizophrenia

The idea that the pathophysiology of schizophrenia might be attributable to NMDAR hypofunction was originally based on clinical observations that NMDAR antagonists, such as phencyclidine and ketamine, transiently reproduced key clinical features of schizophrenia.[8] Attempts to demonstrate that this hypofunction was due to lower levels of NMDAR in the brains of deceased individuals with schizophrenia have produced mixed results, with variable alterations in transcript and protein expression depending upon the NMDAR subunit and cortical area examined,[9] findings that contrast with the highly consistent evidence for alterations of cortical GABA synthesis in schizophrenia.[5]

In contrast, convergent lines of evidence suggest that NMDAR hypofunction in schizophrenia might reflect dysregulation of the receptor rather than a deficit in the number of NMDARs.[10] A variety of postmortem findings, albeit not yet widely replicated, are consistent with this idea. For example, schizophrenia has been associated with (1) alterations in the levels of NMDAR-associated postsynaptic proteins[11]; (2) less NMDAR-mediated signaling following neuregulin 1 activation of ErbB4 receptors[12]; (3) reduced levels of glutathione which modulates the redox-sensitive site of NMDARs[13]; and (4) downregulation of kynurenine 3-monooxygenase which could lead to elevated levels of kynurenic acid, an NMDAR antagonist.[14]

The idea of an NMDAR dysregulation in schizophrenia is also indirectly supported by the findings that the protein products of a number of putative risk genes for schizophrenia can affect NMDAR function.[15] For example, allelic variants in both the neuregulin 1 and ErbB4 genes have been associated with an increased risk for schizophrenia,[15] their gene products have been reported to be increased in the illness,[16] and a gain of function in neuregulin 1-ErbB4 signaling has been shown to suppress NMDAR upregulation.[17] In addition, the gene encoding GluN2B subunits has been implicated as a risk gene for schizophrenia in a recent meta-analysis.[18] Finally, both preclinical studies and some clinical trials suggest that NMDAR-enhancing agents might reduce the severity of certain clinical symptoms of schizophrenia.[19]

Role of PV-Positive Basket Neurons in Production of Gamma Oscillations

As reviewed elsewhere,[7,20,21] GABA-mediated inhibition is a very efficient way of synchronizing large numbers of cortical pyramidal neurons, and particular subclasses of GABA neurons are preferentially involved in generating inhibition-based rhythms. For example, GABA neurons targeting the perisomatic pyramidal cell membrane (proximal dendrites, soma and axon initial segment) may be strongly inhibitory because they synapse near the proximal axon, where action potentials are usually triggered. Three subtypes of perisomatic-targeting GABA neurons are prominent in cortical circuits (figure 1): PV-positive and cholecystokinin-positive basket cells (PVBCs and CCKBCs) and PV-positive chandelier cells (PVChCs). Among these, interestingly, PVChCs may not participate in gamma rhythm mechanisms because their GABAergic inputs onto the axon initial segment appear to be excitatory.[22] CCKBCs are inhibitory but their synapses release GABA in a desynchronized manner[23] that is imprecise for gamma-band synchronization. Consistent with their lack of contribution to gamma oscillations, PVChC and CCKBC synapses onto pyramidal neurons are insensitive to pharmacological manipulations that abolish gamma oscillations.[24] Furthermore, PVChC
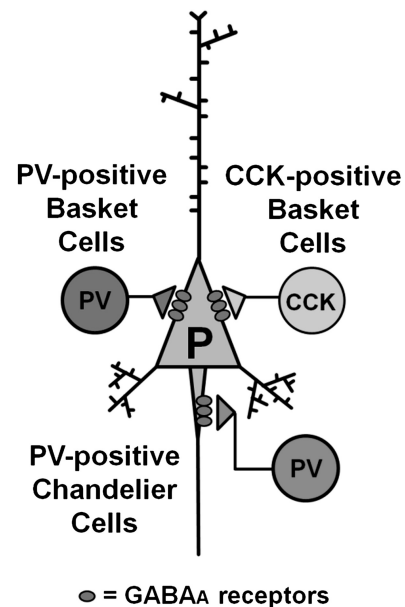

Fig. 1. Major subtypes of perisomatic-targeting gamma-amino butyric acid (GABA) neurons in cortical circuits. Both parvalbumin (PV)-positive and cholecystokinin (CCK)-positive basket cells (green and yellow, respectively) target the soma and proximal dendrites of the pyramidal cell membrane. PV-positive chandelier cells (red) target the axon initial segment. These 3 GABA neuron subtypes signal via GABA$_A$ receptors, although different GABA$_A$ receptor subtypes may mediate the response to GABA at each type of synapse (not shown in the scheme). As described in the main text, current data suggest that gamma oscillation production depends mostly on pyramidal neuron inhibition by PV-positive basket cells.

and CCKBC activity is weakly coupled to the gamma oscillation rhythm.[25] In contrast, synapses from PVBCs are inhibitory[22] and are highly sensitive to pharmacological compounds that abolish gamma oscillations,[24] as expected for inputs involved in gamma rhythm production. Optogenetic experiments also suggest a crucial role of PV neurons in gamma oscillations,[3,4] although whether this approach preferentially targeted PVBCs could not be determined.

Role of Glutamate-Mediated Excitation in Circuit Models of Gamma Oscillations

Two main circuit models have been proposed for the mechanisms producing rhythmic PVBC activity during gamma oscillations (figure 2).[20] In the Interneuron Network Gamma (ING) model, oscillations depend on mutual inhibition between reciprocally connected GABA neurons; that is, interneurons are driven by continuous (tonic) excitatory currents and are synchronized rhythmically by their mutual inhibitory inputs.[20] In ING, pyramidal cells are synchronized rhythmically by the interneuron network but are not directly involved in rhythm production (figure 2). In the second model, termed Pyramidal Interneuron Network Gamma (PING), oscillations depend on the interplay between
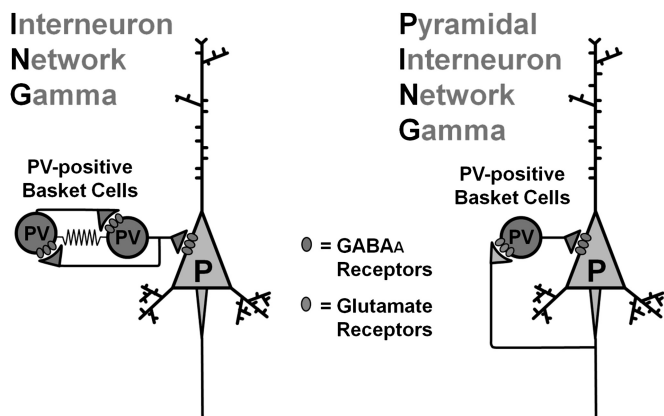
Interneuron
Network
Gamma

Pyramidal
Interneuron
Network
Gamma

PV-positive
Basket Cells

PV-positive
Basket Cells

= GABA_A
Receptors

= Glutamate
Receptors

Fig. 2. Two different circuit-based models for gamma oscillation production. In the Interneuron Network Gamma (ING) model (left panel), the oscillation depends on reciprocal inhibitory interactions between parvalbumin (PV)-positive basket cells. Some form of continuous (tonic) excitatory current is the main source of interneuron activation in ING. Important for the ING model are the electrical gap-junction connections (zig-zag wires) between PV-positive basket cells. In ING, pyramidal cells are synchronized rhythmically by the interneuron network but are not directly involved in rhythm production. In the Pyramidal Interneuron Network Gamma (PING) model (right panel), oscillations depend on the interplay between pyramidal cells and gamma-amino butyric acid neurons via recurrent synaptic connections. In PING models, interneurons are driven by the phasic (synaptic) excitatory glutamate–mediated currents arriving from the pyramidal cells, which are synchronized rhythmically by feedback inhibition. Monosynaptic excitation from pyramidal cells is the main source of interneuron activation in PING. Therefore, in PING, pyramidal cells are directly involved in the gamma rhythm mechanisms. As reviewed in the main text, some current data favor the PING over the ING model.

pyramidal cells and GABA neurons via recurrent synaptic connections.[20] In PING models, interneurons are driven by the phasic (synaptic) excitatory glutamate–mediated currents arriving from the pyramidal cells, which are synchronized rhythmically by feedback inhibition (figure 2). Monosynaptic excitation from pyramidal cells is the main source of interneuron activation in PING.

Computational simulations in networks of artificial neurons may generate gamma oscillations via either ING or PING mechanisms. Interestingly, whereas the mechanisms producing gamma synchrony in cortical networks are still poorly understood, findings from both in vivo and in vitro experimental studies favor the PING model.

Since in the PING model, phasic excitatory input from pyramidal neurons is the main source of interneuron excitation, during the gamma cycle, the pyramidal cell population should fire first, followed by interneurons firing with a delay consistent with monosynaptic excitation. Recordings of the timing of neuronal firing during the gamma oscillation cycle in fact demonstrated such a pattern of firing for pyramidal cells and interneurons in vivo[26,27] and as well as in in vitro studies where the interneurons were identified as PVBCs.[28]

Additional support for the PING model was obtained from studies of genetically modified mice. For example, in mice with a deletion of GABA_A receptors selectively from PV-positive cells, synaptic inhibition of PVBCs, which is required in the ING model, is completely abolished.[29] Interestingly, in a manner inconsistent with ING, these mice display deficits in theta oscillations but have intact gamma oscillations.[29] On the other hand, in mice with a deletion of AMPARs selectively in PV-positive cells,[30] synaptic excitation of PVBCs is strongly reduced, and gamma oscillation power is severely depressed.[30] Such an effect of AMPAR deletion is expected if PING mechanisms mediate gamma rhythm production because AMPARs are highly efficient at mediating the phasic excitation that drives PV neuron activity in PING. In contrast, AMPARs cannot mediate the tonic excitation of PV neurons in ING because they are rapidly and strongly desensitized when tonically exposed to glutamate. Therefore, several lines of evidence support the idea that phasic activation of synaptic glutamate receptors in PVBCs is crucial for gamma rhythm production, as in PING models.

Roles of NMDAR- and AMPA-Mediated Glutamate Synaptic Transmission in Gamma Oscillations

AMPA and NMDA are the main receptor subtypes at cortical and subcortical glutamate synapses, where they coexist in the postsynaptic density and are activated nearly simultaneously by synaptically released glutamate. The AMPAR/NMDAR ratio varies during development and with synaptic plasticity and may characterize subtypes of glutamate synapses. What distinctive functional properties are conferred by NMDARs vs AMPARs?

NMDAR and AMPAR currents differ in at least 3 fundamental properties (figure 3). First, at the resting potential or depolarized potentials below firing threshold, NMDAR channels are largely blocked by magnesium ions, whereas AMPAR channels are not. Their voltage-dependent magnesium block makes NMDARs unlikely to initiate neuronal excitation on their own, unless the synaptic membrane is depolarized via AMPARs or voltage-dependent channels. Second, NMDAR channels typically are highly permeable to calcium, unlike most AMPAR channels subtypes. The high calcium permeability of NMDARs is crucial for induction of synaptic plasticity because NMDAR-mediated calcium influx activates calcium-calmodulin kinase II-alpha, which mediates NMDAR-dependent changes in synaptic strength. Third, in response to synaptic glutamate, NMDARs generate significantly longer currents (~100–400 ms) than AMPARs (~2–10 ms). The long-lasting NMDAR–mediated currents generate a prolonged time window of increased excitability, leading to delayed action potential firing.[31,32]

Since the PING model is favored by recent findings, a key issue is the relative role of NMDARs and AMPARs

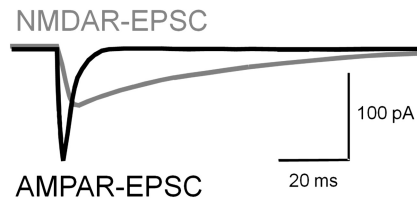NMDAR-EPSC

AMPAR-EPSC

100 pA

20 ms

Fig. 3. Properties of *N*-methyl-D-aspartate receptor (NMDAR)- and AMPAR-mediated excitatory synaptic currents (EPSCs). Various properties distinguishing NMDAR-EPSCs and AMPAR-EPSCs are described in the main text. Especially, important for models of gamma oscillations is the much shorter duration of the AMPAR-EPSC relative to the NMDAR-EPSC. Whereas short-lasting AMPAR-EPSCs are sufficient to support robust gamma oscillations,[31] long-lasting NMDAR-EPSCs produce asynchronous and delayed postsynaptic interneuron firing[32] that is not locked to the incoming inputs from pyramidal cells[31] and in a PING model of gamma oscillations reduces gamma oscillation power.[31] Such an inverse relation between gamma power and NMDAR contribution[31] suggests that the reduction of NMDAR contribution at synapses onto parvalbumin (PV)-positive basket cells that occurs during normal postnatal development[33,34] helps optimize gamma oscillation production during cortical circuit development. Thus, during gamma oscillations in adult cortex, PV-positive basket cells appear to be mostly driven by fast AMPAR-mediated excitation. See main text for additional details.

in the synaptic activation of PVBCs in general and particularly during gamma oscillations. Studies of neuronal activity in the prefrontal cortex of awake rats showed that NMDARs may be crucial to drive inhibitory interneuron activity.[35] In such studies, systemic NMDAR antagonist administration enhanced pyramidal cell firing and decreased the activity of putative GABA neurons,[35] suggesting that NMDAR blockade leads to pyramidal cell disinhibition. However, in such recordings in awake animals, identification of neurons is challenging and relies on measuring extracellular action potential duration, which is typically shorter for interneurons than pyramidal cells, as determined for the NMDAR antagonist-sensitive interneurons.[35] Because GABA neurons are extremely diverse and most of the subclasses have shorter action potentials than pyramidal cells, it is not clear if the NMDAR antagonist-sensitive interneurons recorded in awake animals include the PVBCs, whose activity is crucial for gamma oscillation production.

Using in vitro recordings, PVBCs can be easily distinguished from pyramidal cells and from other interneuron subtypes based on their electrophysiological and morphological properties. Interestingly, results from in vitro studies suggest that, compared with pyramidal cells, NMDAR contribution to synaptic activation of PV-positive neurons is relatively modest. For example, in PVBCs from various cortical regions, excitatory postsynaptic potentials (EPSPs) display minimal NMDAR contribution at subthreshold membrane potentials.[31,36] Similarly, NMDAR contribution to excitatory postsynaptic currents (EPSCs) in PVBCs is weaker than in pyramidal cells.[31,33,36] Driving PVBCs to fire action potentials

from rest is significantly more dependent on AMPARs than on NMDARs, compared with pyramidal neurons.[31] Consistent with these physiological findings, electron microscopy studies have shown low levels of NMDAR subunits in glutamate synapses onto PV-positive cells.[37] Finally, the AMPAR/NMDAR ratio in synapses onto PV-positive neurons suggests a ~3 times stronger AMPAR than NMDAR contribution,[27,31,33,36,38] a significantly higher ratio than in pyramidal cells.

As mentioned, NMDAR-mediated currents have the following 3 distinctive properties: voltage-dependent magnesium block, high calcium permeability, and long-lasting EPSCs. Studying these properties in synaptic responses in PVBCs revealed a number of features consistent with relatively weak NMDAR contribution. First, NMDAR magnesium block is stronger in PVBCs than in excitatory neurons,[36] weakening NMDAR contribution to EPSP-spike coupling in PVBCs.[36] Second, glutamate synapses generate intracellular calcium transients that are less sensitive to NMDAR antagonists in PV-positive neurons than in pyramidal cells or other interneuron subtypes.[39] Third, synaptically evoked calcium transients in PVBCs are short lasting and sensitive to blockers of the GluA2 subunit-lacking AMPARs,[39] which are, atypically for AMPARs, calcium permeable. Whereas the data reviewed above suggest that the NMDAR contribution at glutamate synapses onto PV cells is relatively weak, it is possible that the calcium permeability conferred by NMDARs plays some role independent of directly mediating PV cell excitation. For instance, it is well established that calcium influx through the NMDAR channel participates in the mechanisms of long-term synaptic plasticity. Interestingly, consistent with weak calcium influx through NMDARs, long-term potentiation at glutamate synapses onto PVBCs is NMDAR independent,[40,41] even though the same stimulation protocols produce NMDAR-dependent long-term potentiation in pyramidal cells.[40] Moreover, long-term potentiation at glutamate synapses onto PVBCs is enhanced by postsynaptic hyperpolarization,[41] which increases NMDAR channel magnesium block but enhances calcium influx via GluA2-lacking AMPARs.[41] Therefore, additional research is necessary to determine the role of calcium influx through NMDAR channels at synapses onto PV neurons.

Compared with pyramidal neurons and other interneuron subtypes, EPSCs in PVBCs are short lasting.[31,33] Interestingly, the purely AMPAR-mediated EPSCs (measured after NMDARs are blocked) have shorter duration in PVBCs compared with pyramidal neurons.[31] Among AMPARs, the GluA2-lacking subtype determines the shortest AMPAR-EPSC duration, and, interestingly, GluA2-lacking AMPARs were shown to mediate short-lasting AMPAR-EPSCs in PVBCs.[33,34] Among NMDARs, the GluN2A subunit–containing subtype determines the shortest NMDAR-EPSC duration, and,

interestingly, PV-positive neurons express higher Glu-N2A/GluN2B subunit ratio than pyramidal cells.[42] Thus, the AMPAR/NMDAR ratio and subunit composition of AMPARs and NMDARs in PVBCs suggest that their glutamatergic synaptic inputs are optimized for very fast activation. In fact, synaptic activation of PVBCs is extremely fast,[43] apparently due to specific biophysical properties of their synapses and dendrites.[43]

Interestingly, the NMDAR antagonist MK801 applied acutely to brain slices from the posterior cingulate or retrospenial cortices, decreases the frequency of IPSCs in pyramidal cells.[44] Furthermore, prolonged exposure to ketamine in vivo decreases inhibitory postsynaptic current (ISPC) frequency in pyramidal cells recorded in prefrontal cortex slices.[45] NMDAR antagonists suppress disynaptic IPSPs evoked by stimulation of excitatory inputs onto hippocampal pyramidal cells,[46,47] but similar disynaptic IPSPs evoked in neocortical pyramidal neurons are insensitive to NMDAR antagonists.[31,46] Whereas the results reviewed above support the idea that NMDAR antagonists decrease inhibition onto pyramidal cells in some cortical regions, the interneuronal source of the IPSCs sensitive to NMDAR antagonism was not identified in such previous studies.[44,45,47] Because several studies reviewed here suggest that NMDAR contribution to synaptic activation of PV neurons is weak, an interesting possibility is that the NMDAR antagonist-induced disinhibition is mediated by interneurons of some class different from the PV cells. For instance, in vivo exposure to ketamine increases IPSCs in pyramidal cells in the prefrontal cortex of 3-month-old but not of 1-month-old rats.[45] Such findings are inconsistent with reports showing that the NMDAR contribution in synapses onto PV neurons is strong in the immature prefrontal cortex but is weak in mature prefrontal cortex.[31,33,34]

Effects of NMDAR Antagonism on Gamma Oscillations

In the favored PING model for circuit mechanisms of gamma oscillations (see "Role of Glutamate-Mediated Excitation in Circuit Models of Gamma Oscillations" section), weakening the activation of PVBCs by pyramidal neurons would significantly reduce PVBC recruitment and thus gamma oscillation power. Consistent with this prediction, genetically engineered deletion of AMPARs selectively from PVBCs markedly impairs gamma oscillations.[30] However, since the NMDAR contribution to PVBC activation is relatively modest, does NMDAR antagonism or hypofunction affect gamma oscillation production? To address this issue, we built a computational model network of artificial pyramidal cells and interneurons generating gamma oscillations via PING-like mechanisms.[31] In this network, fast AMPAR–mediated excitation of PVBCs produced a robust gamma rhythm.[31] In contrast, we observed an inverse relation between NMDAR contribution and gamma power such that increasing NMDAR currents decreased gamma-band power.[31] In the model, consistent with experimental observations,[32] the introduction of long-lasting NMDAR currents in synapses onto PVBCs produced firing of delayed action potentials that were not locked to the excitation arriving from the pyramidal cells,[31] and such additional asynchronous firing of some PVBCs decreased gamma power.[31] Our simulations therefore predict that, if the NMDAR contribution at inputs onto PVBCs is normally low, then further reducing NMDAR contribution would not decrease gamma oscillation power. In fact, NMDAR antagonists acting on PVBCs would be predicted to somewhat enhance gamma-band activity.

Consistent with these computational modeling findings, gamma oscillations in hippocampal or neocortical brain slices were reduced or abolished by AMPAR antagonists but were unaffected by NMDAR antagonists in most studies (see references in Rotaru et al[31]). In entorhinal cortex slices, the NMDAR antagonist ketamine did not alter gamma power in layers 4–5 but reduced gamma power in layer 2.[48] In primary auditory cortex, ketamine increased gamma power.[48] The results of most in vitro studies therefore suggest that the NMDAR contribution to PVBC activation during the gamma cycle is relatively modest. However, ketamine, in addition to blocking NMDARs, has several other pharmacological effects that limit its utility for testing the role of NMDARs in PVBCs.

Several studies of gamma oscillations recorded in vivo in animal models found that NMDAR antagonists increase basal gamma oscillation power.[49,50] Ketamine also enhanced gamma oscillation power in healthy human subjects.[51] Although in vivo studies clearly have advantages over in vitro studies, the systemic administration of NMDAR antagonists simultaneously affects NMDARs in multiple brain regions and various cell types within a region, limiting the interpretation of findings in terms of the role of NMDARs in PVBCs.

To model NMDAR hypofunction in vivo, an alternative approach to systemic administration of antagonists is cell-type specific, genetically engineered reduction of NMDAR expression. Recently, mice were generated with an ablation of the NMDAR subunit GluN1 restricted to PV-positive neurons (PV-GluN1$^{-/-}$ mice).[27,38] In the hippocampus of awake freely moving PV-GluN1$^{-/-}$ mice, theta oscillation power and theta modulation of gamma oscillation amplitude were decreased, but gamma power was increased.[27] Similarly, gamma oscillations were enhanced in somatosensory cortex of anesthetized or awake PV-GluN1$^{-/-}$ mice.[38]

Overall, the in vitro and in vivo pharmacological studies and experiments in PV-GluN1$^{-/-}$ mice do not support the idea that NMDARs mediate PVBC recruitment during gamma oscillations. In fact, the findings that NMDAR hypofunction increases gamma power suggest the opposite.

Conclusions

In concert, the findings reviewed above raise an important question regarding the mechanisms by which NMDAR hypofunction could contribute to the neural substrate for cortical circuit dysfunction in schizophrenia. Specifically, given that NMDARs appear to make a small contribution to activation of PVBCs, how could impaired NMDAR regulation contribute to the alterations in markers of PVBC function (eg, lower levels of PV and glutamic acid decarboxylase 67 mRNAs) observed in schizophrenia? The idea that the effects are not directly mediated by NMDARs on mature PVBCs is supported by findings that neither mice deficient in serine racemase, which produces the endogenous NMDAR coagonist D-serine, nor the chronic administration of ketamine or phencyclidine to adult mice or rats, resulted in altered phenotype of PV neurons.[52] Interestingly, glutamate inputs onto immature PV neurons display a significant NMDAR contribution, which declines during development until reaching low levels in adulthood.[33,34] Moreover, early postnatal ablation of NMDAR subunits from PV neurons produces behavioral abnormalities that are not observed if the ablation is produced postadolescence.[53] Therefore, NMDAR antagonists may affect the phenotype of PV neurons if delivered early in development when these neurons have high levels of NMDAR. This view would suggest that the NMDAR hypofunction must arise early in development in individuals who do not manifest the diagnostic psychotic features of schizophrenia until years or decades later. This interpretation might provide the neural substrate for the findings that certain cognitive abnormalities reflective of cortical dysfunction are present during childhood in persons later diagnosed with schizophrenia.[54]

Alternatively, cortical NMDAR hypofunction in schizophrenia may be mediated by NMDAR on pyramidal neurons, other classes of GABA neurons or neurons that furnish projections to the cortex. This interpretation is supported by some experimental models. For example, genetic manipulations that lower the expression levels of the schizophrenia risk gene dysbindin, which exhibits lower mRNA and protein levels in schizophrenia, leads to lower NMDA currents in cortical pyramidal cells, and impaired cognition.[55]

Thus, although substantial evidence supports a role for dysregulation of NMDARs in the pathophysiology of schizophrenia, additional research is required to determine the particular cell type(s) that mediate dysfunctional NMDAR signaling in the illness.

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