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The role of glutamatergic inputs onto parvalbumin-positive interneurons: relevance for schizophrenia

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Abstract

Cognitive impairment, a core feature of schizophrenia, has been suggested to arise from a disturbance of gamma oscillations that is due to decreased neurotransmission from the parvalbumin (PV) subtype of interneurons. Indeed, PV interneurons have uniquely fast membrane and synaptic properties that are crucially important for network functions such as feedforward inhibition or gamma oscillations. The causes leading to impairment of PV neurotransmission in schizophrenia are still under investigation. Interestingly, NMDA receptors (NMDARs) antagonism results in schizophrenia-like symptoms in healthy adults. Additionally, systemic NMDAR antagonist administration increases prefrontal cortex pyramidal cell firing, apparently by producing disinhibition, and repeated exposure to NMDA antagonists leads to changes in the GABAergic markers that mimic the impairments found in schizophrenia. Based on these findings, PV neuron deficits in schizophrenia have been proposed to be secondary to (NMDAR) hypofunction at glutamatergic synapses onto these cells. However, NMDARs generate long-lasting postsynaptic currents that result in prolonged depolarization of the postsynaptic cells, a property inconsistent with the role of PV cells in network dynamics. Here, we review evidence leading to the conclusion that cortical disinhibition and GABAergic impairment produced by NMDAR antagonists are unlikely to be mediated *via*NMDARs at glutamatergic synapses onto mature cortical PV neurons.

Keywords

cognition; GABA; NMDA; oscillations

Introduction

The neural basis underling the well-described cognitive deficits of schizophrenia (Censits et al., 1997; Mohamed et al., 1999; Heaton et al., 2001; Gold, 2004) has been under intense investigation over the past years and several new hypotheses have recently been proposed (Lewis, 2010).

It has been suggested that normal cognitive function depends on cortical oscillatory activity and especially on gamma band synchronization (Gray et al., 1989; Fries et al., 2001b, 2007; Pesaran et al., 2002; Bichot et al., 2005; Womelsdorf et al., 2006) in distributed networks

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across the neocortex. Synaptic inhibition in cortical circuits, mediated by various inhibitory GABAergic interneurons, is crucially implicated in the mechanisms that generate and maintain neural oscillations (Traub et al., 2004; Fries et al., 2007). In particular, the mechanisms generating synchrony in the gamma band have been strongly linked to the activity of GABAergic interneurons of the parvalbumin (PV)-containing class (Klausberger and Somogyi, 2008; Cardin et al., 2009).

Substantial evidence suggests that cortical GABAergic neurotransmission is altered in schizophrenia, especially including alterations of PV-positive cells (Lewis, 2010). Thus, although other neural mechanisms are also likely to contribute to cognitive deficits in schizophrenia, an attractive hypothesis suggests that such deficits derive from an impairment of gamma band synchrony which is caused by alterations in PV neuron-mediated inhibition (Gonzalez–Burgos et al., 2010; Lewis, 2010; Lewis et al., 2011). However, the mechanisms producing alterations in GABA neurons in general, and in PV neurons in particular, in schizophrenia are still unclear (Lewis, 2010).

Early observations of the effects of NMDA receptor (NMDAR) antagonists in healthy human subjects and in psychiatric patients showed that these antagonists mimic or exacerbate core symptoms of schizophrenia, including cognitive deficits (Javitt and Zukin, 1991; Javitt, 2009). Based on these observations, it was suggested that hypofunction of NMDAR-mediated signaling may be a potential pathological mechanism in the schizophrenia disease process. However, because NMDARs are ubiquitous in cortical and subcortical brain regions and are expressed by many different cell types within each region, the cellular substrates of the effects of NMDAR antagonists or NMDAR hypofunction in schizophrenia have remained elusive.

It has been suggested that NMDAR hypofunction is an upstream cause of alterations of PV neurons in schizophrenia (Coyle, 2006; Lisman et al., 2008). NMDAR hypofunction could lead to PV neuron abnormalities in schizophrenia *via* several direct and indirect mechanisms (Lewis and Gonzalez-Burgos, 2006). An interesting possibility is that NMDARs at glutamatergic synapses onto PV neurons are crucial for their activation and therefore NMDAR hypofunction produces PV neuron hypoactivity (Seamans, 2008).

Here, we review studies addressing the importance of NMDARs for the activation of PV neurons in cortical circuits in the context of the role of PV neurons in the production of synchronized gamma band oscillations, and the resulting cognitive deficits, in schizophrenia.

The importance of synchronized prefrontal cortex activity for cognitive function

Cognitive control implies the coordination of incoming sensory and motor information with representations of internal goals and rules to facilitate a context-appropriate behavioral response that can serve adaptive functions (Miller, 2000; Miller and Cohen, 2001; O'Reilly, 2006). Many of the brain regions involved in such coordination show structural and functional abnormalities in schizophrenia (Meyer-Lindenberg, 2010). The dorsolateral prefrontal cortex (PFC), which is extensively interconnected with cortical and subcortical regions, is thought to be crucial for cognitive control by exerting top-down control of the flow of neural activity between brain regions (Miller, 2000; Miller and Cohen, 2001). Importantly, subjects with schizophrenia have deficits in cognitive control that may involve PFC dysfunction (Cho et al., 2006; Lesh et al., 2011).

How top-down control influences sensory processing and perception is still under investigation, but the so-called temporal binding hypothesis (Engel et al., 1992; Von der

Malsburg, 1994; Singer and Gray, 1995; Roelfsema et al., 1996; Singer, 1999; Engel and Singer, 2001) suggests that neural synchrony with precision in the millisecond range is crucial for object representation, response selection, attention and sensorimotor integration. Synchronized or correlated neuronal discharge produces a much stronger impact on the neurons in the target areas (Von der Malsburg, 1994) as opposed to the temporally disorganized ones that tend to fail to elicit a significant response (Abeles, 1982; Alonso et al., 1996; Konig et al., 1996). As a consequence, synchrony can enhance response saliency and can select and group subsets of neuronal responses for further joint processing. Therefore, synchronized assemblies of neurons in association cortices would carry an abstract value of the representations from primary sensory areas with importance in guiding selective feature representation.

If the formation of synchronized neuronal assemblies in PFC and other cortical regions is crucial to cognitive function *via* top-down pathways, then it is important to understand the mechanisms producing neuronal synchrony. Interestingly, the selective recruitment of GABA-mediated synaptic inhibition that leads to precise control of pyramidal cell firing, ultimately results in rhythmic cortical activity at different oscillatory frequencies (Buzsaki and Draguhn, 2004; Buzsaki et al., 2004; Fries, 2009). Among the synchronized rhythms in the brain, gamma band (30 – 80 Hz) oscillations are present in behavioral states ranging from simple sensory stimulation (Gray et al., 1989) to attentional selection (Fries et al., 2001a,b; Bichot et al., 2005; Womelsdorf et al., 2006) and working memory maintenance (Pesaran et al., 2002). Patients with schizophrenia show deficits across all sensory modalities which can impact upstream cortical processing with consequences in higher order cognitive operations (Javitt, 2009; Arguello and Gogos, 2010). Moreover, the deficits in cognitive control exhibited by subjects with schizophrenia are correlated with deficits in gamma oscillation production (Cho et al., 2006; Lesh et al., 2011).

The role of GABAergic neurons in cortical circuit function

The temporal regulation of the activity of pyramidal cells (White, 1989; Whittington and Traub, 2003; Markram et al., 2004), which are much more abundant than interneurons, is achieved *via* division of labor among a rich diversity of GABAergic interneuron subtypes (Wang et al., 2004; Soltesz, 2006). The remarkable variability in the molecular, anatomical and physiological features of GABAergic interneurons renders their functional classification extremely difficult (Ascoli, 2008). The specific subgroup of interneurons called the fast spiking (FS) cells are reliably differentiated from other interneuron subtypes (non-fast spiking; NFS) based on their electrical properties and the presence of the calcium binding protein PV, which is not contained in any of the NFS interneuron subtypes (Freund, 2003). The two morphological subtypes of FS PV cells, the basket and the chandelier cells, innervate the vicinity of the somatic membrane compartment of the target pyramidal neurons in close proximity to the axon initial segment (Somogyi, 1977; Halasy et al., 1996; Somogyi et al., 1998; Somogyi and Klausberger, 2005), which contributes to action potential generation. Thus, these two cell types exercise precise control of the neuronal output by dictating whether already processed information from the entire dendritic tree of the pyramidal cells can be transmitted to other neurons. Interestingly, whereas PV basket cells are inhibitory, chandelier neurons appear to be excitatory (Szabadics et al., 2006; Woodruff et al., 2010) suggesting fundamentally different roles for these two morphological subtypes of PV neurons. Moreover, PV basket cells contact a vast number of postsynaptic cells and are thus able to temporally regulate the firing of large groups of neurons (Cobb et al., 1995; Pouille and Scanziani, 2001). This specific wiring of PV and pyramidal cells leads to one important functional consequence which is the establishment of neural oscillations and synchrony within cortical networks (Gray et al., 1989; Neltner et al., 2000; Destexhe et al., 2003; Wang et al., 2003). By contrast, many of the NFS interneuron subtypes synapse in

close contact to excitatory inputs arriving along the pyramidal dendritic tree, a location which enables them to regulate synaptic plasticity or integration of inputs from specific brain regions.

PV GABA neuron-dependent cortical oscillations: importance of pyramidal cell-interneuron connections

In the cortex and the hippocampus, rhythmic firing is an emergent property of interactions between excitatory pyramidal cells and inhibitory interneurons (Whittington et al., 2000). Activation of excitatory cells leads to excitation of inhibitory interneurons which then act to inhibit further excitation. As inhibition wears off excitatory cells are free to fire again (Whittington et al., 2000). Thus, inhibitory neurons firing synchronously are effective in defining a window in which the excitatory cells can fire. Although the specific gamma band synchronization can emerge in any network of excitatory and inhibitory neurons, certain basic prerequisites must be fulfilled (Tiesinga et al., 2001; Börgers et al., 2005). Among these requirements, the time constant of synaptic currents mediating the excitation-inhibition neurotransmission is one of the most important determinants of the gamma rhythms (Vida et al., 2006; Bartos et al., 2007). The fast period of the gamma cycle implies the presence of a short window of opportunity for the excitatory neurons to fire when inhibition wears off and the next inhibitory input arrives (Hasenstaub et al., 2005). To reliably generate this window of opportunity, the phasic excitation of interneurons is thought to be required for gamma oscillations (Hájos and Paulsen, 2009; Whittington et al., 2011). Excitatory inputs must be strong enough to drive inhibitory cells to fire with high precision and low variability which can be achieved by producing a reliable excitatory postsynaptic potential (EPSP)-spike coupling mechanism implemented *via* strong predominantly AMPA receptor (AMPAR)-mediated glutamatergic inputs onto inhibitory cells. The strongly driven inhibitory cell will provide inhibition to numerous postsynaptic targets including both pyramidal cells and other interneurons cells. The synaptic input from the interneuron to the excitatory neurons must strongly inhibit pyramidal cells, but only for a short period of time, and this is mediated by $GABA_A$ receptors with fast kinetics as determined by their specific subunit composition (Bartos et al., 2007).

Such ‘clocking’ networks (Buzsaki and Draguhn, 2004) can be brought about by the FS PV cells specifically because of their anatomical and functional connections with pyramidal cells and other interneurons. In fact, among all the GABAergic cell subtypes, FS PV neurons are thought to play a crucial functional role in the generation and maintenance of synchronous gamma oscillations, as demonstrated in different types of studies (Sik et al., 1995; Joho et al., 1999; Gloveli et al., 2005; Klausberger and Somogyi, 2008; Cardin et al., 2009; Sohal et al., 2009; Carlen et al., 2011; Korotkova et al., 2011).

GABAergic deficits in patients with schizophrenia

Cognitive impairment in patients with schizophrenia is accompanied by altered activation of the dorsolateral prefrontal cortex (DLPFC) (MacDonald et al., 2005; Van Snellenberg et al., 2006). Moreover, cognitive deficits in schizophrenia correlate with decreased power and synchrony of gamma oscillations (Bichot et al., 2005; Gonzalez-Burgos et al., 2010; Uhlhaas and Singer, 2010). Because, as mentioned above, GABA neuron activity appears to be crucial for gamma band synchrony, it is interesting to speculate that alterations of GABA neurons in schizophrenia may underlie the deficits of cognitive function.

In parallel with studies investigating cognitive function in patients with schizophrenia, postmortem studies performed over the past three decades have consistently found reduced levels of the GABA synthesizing enzyme, glutamic acid decarboxylase 67 (GAD67), in the

DLPFC of subjects with schizophrenia (Bird et al., 1978; Hanada et al., 1987; Simpson et al., 1989; Akbarian et al., 1995; Benes et al., 1996; Guidotti et al., 2000; Mirnics et al., 2000; Volk et al., 2000; Hashimoto et al., 2005, 2007, 2008; Straub et al., 2007; Mellios et al., 2009; Duncan et al., 2010; Curley et al., 2011). The predicted resulting deficit in GABA synthesis in schizophrenia may lead to dysfunctional activation of the $GABA_A$ receptors at the postsynaptic targets of the inhibitory inputs. Consequently, if synchronization is indeed a major role of GABA-mediated synaptic inhibition, then disinhibition of the postsynaptic target neurons would produce temporally less organized pyramidal cells firing, leading to decreased synchrony, impaired information processing and therefore cognitive dysfunction.

Importantly, in schizophrenia (Lewis et al., 2005; Lewis, 2010) lower levels of GAD67 mRNA are particularly prominent in the PV interneurons (Hashimoto et al., 2003), whereas other GABA neurons exhibit normal levels of GAD67 mRNA (Akbarian et al., 1995; Volk et al., 2000). In addition, expression of the $GABA_A$ receptor $\alpha 1$ subunit is also preferentially lower in pyramidal neurons at the postsynaptic inputs from PV interneurons (Glausier and Lewis, 2011). These impairments in PV neurotransmission can be responsible for the dysfunctional changes in gamma band oscillations in brains of subjects with schizophrenia.

Whereas decreased inhibitory drive from PV cells onto their postsynaptic targets could be a core pathophysiological feature of schizophrenia, the mechanism implicated in the PV dysfunction are still under investigation. There are several ways in which GABAergic transmission in a network may be reduced. For instance, an impairment of excitatory drive onto inhibitory cells would lead to decreased firing of the interneurons and deficit GABA release on the postsynaptic targets. Furthermore, a decrease in GABAergic transmission can be the result of a morphological loss of neurons or inhibitory inputs, whereas the recruitment of these cells remains intact. Finally, lower levels of released GABA or lower numbers of postsynaptic $GABA_A$ receptors can be alternative mechanisms of impaired transmission.

The NMDA receptor antagonist model of schizophrenia: relevance for GABAergic deficits in schizophrenia

Several NMDA receptor antagonists, including ketamine, dextromethorphan, phencyclidine and nitrous oxide (N_2O) are popular as recreational drugs for their dissociative, hallucinogenic and/or euphorizant properties. These compounds also produce behavioral effects that are similar to core symptoms of schizophrenia: in healthy adult subjects, phencyclidine and ketamine produce a schizophrenia-like syndrome, including positive and negative symptoms, and cognitive deficits (Javitt and Zukin, 1991; Krystal et al., 1994; Lahti et al., 1995; Newcomer et al., 1999). These observations have led to the suggestion that hypofunction of NMDAR-mediated signaling is a key feature of the disease process of schizophrenia. Thus, acute systemic NMDAR antagonist administration to adult animals is widely used as a model to study behavioral and neurochemical disruptions that may mimic those produced by NMDAR hypofunction in the disease (Mouri et al., 2007).

Because NMDARs are present at glutamate synapses onto multiple types of neurons in essentially all cortical and subcortical regions, understanding the cellular substrate underling the behavioral effects of NMDAR hypofunction induced by systemic antagonist administration is challenging. Interestingly, experiments recording neuronal activity in the rat prefrontal cortex *in vivo* found that systemic NMDAR antagonist administration increases pyramidal cell activity (Homayoun and Moghaddam, 2007). Moreover, NMDAR antagonists decreased the activity of putative interneurons recorded *in vivo*in similar conditions, leading to the speculation that the antagonists mainly act on GABAergic interneurons, indirectly producing pyramidal cell disinhibition (Homayoun and Moghaddam, 2007). An interesting possibility is that NMDAR hypofunction in

schizophrenia produces disinhibition mostly by reducing the activity of PV neurons (Coyle, 2006; Lewis and Moghaddam, 2006; Lisman et al., 2008; Seamans, 2008). Importantly, such a PV neuron-mediated disinhibition implies that PV cell activation is significantly more sensitive to NMDAR antagonists than pyramidal cell activation. A substantially stronger sensitivity to NMDAR antagonists could be explained by a stronger contribution of NMDARs at glutamatergic synapses onto PV cells or by expression of a pharmacologically different subtype of NMDAR in PV cells.

Supporting the general idea that NMDAR hypofunction could lead to PV neuron dysfunction, some studies found that NMDAR antagonists produce a reduction of PV and GAD67 expression in FS PV cells that mimics the alterations found in schizophrenia (Cochran et al., 2002; Kinney et al., 2006; Behrens et al., 2007). Decreased levels of PV facilitates GABA release (Vreugdenhil et al., 2003) and, thus, as suggested elsewhere (Lewis et al., 2005; Gonzalez-Burgos and Lewis, 2008), decreased PV in schizophrenia may be a compensatory response to a GAD67 deficit that reduces GABA synthesis and release. Therefore, one possibility is that NMDAR antagonists primarily produce a decrease in GAD67 levels which secondarily leads to a compensatory decrease in PV levels. Importantly, because neural activity is the main factor regulating GAD67 expression (Jones, 1990; Akbarian and Huang, 2006), NMDAR antagonists may cause changes in GAD67 and PV through their effects on network activity levels mediated mostly by the firing of pyramidal cells. Cortical network hyperactivity *via* increased firing of pyramidal cells increases GAD67 levels (Liang and Jones, 1997; Esclapez and Houser, 1999) and, conversely, network hypoactivity due to deprivation of afferent activity decreases GAD67 levels and inhibitory synaptic strength (Benson et al., 1994; He et al., 2006; Jiao et al., 2006). It is very important to mention that changes in GAD67 and PV require chronic treatment, in some cases for at least 42 days (Cochran et al., 2003; Behrens et al., 2008; Jenkins et al., 2008; Romon et al., 2011). Indeed, a decrease in GAD67 levels would lead to a decrease in the level of inhibition provided by the GABAergic interneurons, leading consequently to disinhibition of pyramidal neurons, which could constitute a pathological mechanism in schizophrenia. A disinhibition phenomenon was also hypothesized to be present in cortex, but to occur within minutes of NMDAR antagonist administration (Homayoun and Moghaddam, 2007). Under these conditions, GAD67 levels would not be changed. Moreover, due to the activity-dependent mechanisms controlling GAD67 levels, the increased activity of pyramidal cells due to their apparent disinhibition following acute administration of NMDAR antagonists should lead in time to an increase of GAD67 levels. Therefore, it would appear that the NMDAR antagonist-induced alterations in GAD67 and NMDAR antagonist-induced disinhibition are not mechanistically related. In addition, recent findings that subchronic phencyclidine or ketamine treatment in adulthood did not affect PV levels in hippocampus or PFC challenge the hypothesis that pathological deficits in PV expression are simply a consequence of NMDAR hypofunction (Benneyworth et al., 2011).

Properties of glutamatergic inputs onto inhibitory interneurons

The neurotransmitter glutamate acts *via* several ionotropic receptor subtypes including AMPA, kainate and NMDA receptors which produce significantly different effects when activated at the postsynaptic level (Nakanishi et al., 1998). In addition to their well-known role in synaptic plasticity and excitotoxicity (Choi, 1987; Tymianski et al., 1993; Malinow and Malenka, 2002; Hardingham and Bading, 2010), NMDARs may differentially contribute to postsynaptic integration. In pyramidal cells, synaptic NMDAR-mediated currents prolong EPSPs (Hestrin et al., 1990; Cull-Candy and Leszkiewicz, 2004) specifically at depolarized potentials due to the decrease of voltage-dependent Mg^{2+} block of the NMDAR channel (Thomson and West, 1986; Forsythe et al., 1988; Jones and Baughman, 1988; Thomson et al., 1988; Thomson, 1997). Together with NMDARs,

voltage-dependent conductances act at depolarized potentials, to shape the EPSP kinetics allowing integration of inputs over prolonged time windows in pyramidal cells (Stuart and Sakmann, 1995; Magee, 1998; Fricker and Miles, 2000; Galarreta and Hestrin, 2001; Gonzalez-Burgos and Barrionuevo, 2001; Rotaru et al., 2007) or in interneurons (Fricker and Miles, 2000; Maccaferri and Dingledine, 2002).

Crucial for the role of NMDARs on local circuit function and gamma oscillation alterations in schizophrenia are the synaptic mechanisms of GABAergic interneuron activation. Importantly, significant differences have been described in the synaptic inputs onto FS vs. NFS interneurons (Gulyas et al., 1999; Gupta et al., 2000; Porter et al., 2001; Markram et al., 2004; Mátyás et al., 2004) leading to the conclusion that recruitment of FS and NFS is differentially dependent on the network activity level. FS neurons display a remarkably fast synaptic activation (Hu et al., 2010) that precisely follows the presynaptic pyramidal cell activity pattern favoring the integration of coincident inputs (Galarreta and Hestrin, 2001). This may require short-lasting EPSCs, because long-lasting EPSCs produce spikes during prolonged time windows (Fricker and Miles, 2000; Maccaferri and Dingledine, 2002). Fast synaptic activation may involve weak NMDAR contribution, because compared with AMPAR-EPSCs, NMDAR-EPSCs typically are long-lasting (Hestrin et al., 1990; Cull-Candy and Leszkiewicz, 2004). Interestingly, FS neurons in hippocampus and somatosensory cortex actually display short-lasting EPSCs with weak NMDAR contribution (Geiger et al., 1995, 1997; Angulo et al., 1999; Nyiri et al., 2003; Goldberg et al., 2003a; Lamsa et al., 2007; Lu et al., 2007; Hull et al., 2009; Gittis et al., 2010). In contrast, the NFS cells summate and integrate EPSPs over much greater time windows (Glickfeld and Scanziani, 2006), somewhat preventing coincidence detection and favoring temporal integration of synaptic inputs. Moreover, several subclasses of NFS interneurons have strong synaptic NMDAR currents (Lu et al., 2007; Wang and Gao, 2009).

Because FS PV cells mediate temporally precise signaling crucial for their role in gamma oscillations, the composition of synaptic receptors onto these cells is extremely important (Hájos and Paulsen, 2009). Selective knockout of the AMPAR subunits GluA1 or GluA4 from PV cells reduced their phasic excitatory drive (Fuchs et al., 2007). Consequently, GluA1- or GluA4-deficient PV-positive interneurons fired fewer spikes with less temporal precision. In the same knockout mice, the power of gamma oscillations was profoundly decreased (Fuchs et al., 2007). These findings support the hypothesis that recruitment of PV cells *via* AMPAR-containing glutamatergic synapses is necessary for gamma oscillations.

Whereas glutamate inputs onto PV cells in hippocampus and somatosensory cortex appear to primarily depend on AMPARs, whether this is similar in PFC is less well understood. Therefore, we recently assessed the relative contribution of NMDAR to synapses onto FS and pyramidal cells in PFC and found that, as in other cortical regions, FS cells in PFC had weaker NMDAR contribution to EPSCs compared with pyramidal cells (Rotaru et al., 2011). Moreover, the AMPAR-EPSCs in prefrontal FS PV neurons were faster than in pyramidal cells (Rotaru et al., 2011), perhaps due to the predominance of GluA2-lacking, rapidly deactivating AMPARs (Geiger et al., 1997; Angulo et al., 1999; Hull et al., 2009; Nissen et al., 2010; Wang and Gao, 2010). Therefore, synaptic properties and specific biophysical features of their dendrites (Hu et al., 2010) contribute to a fast and temporally precise synaptic activation of FS neurons in various cortical regions including PFC. Indeed, the contribution of NMDAR currents to EPSP-spike coupling is smaller in FS PV neurons compared with pyramidal cells (Karayannis et al., 2007; Rotaru et al., 2011). Thus, overall, FS cell excitation in PFC and other cortical regions is less sensitive to NMDAR antagonists than is pyramidal cell excitation, because FS cells have EPSCs with a weak NMDAR component. The weaker NMDAR component, thus shorter EPSP duration, possibly contributes to the rapid coupling of excitation with inhibitory output (Jonas et al., 2004; Hu

et al., 2010). In fact, pyramidalpyramidal synapses in PFC have robust long-lasting NMDA EPSCs (Wang et al., 2008), which may be crucial for recurrent excitation and working memory (Lisman et al., 1998; Wang, 1999). Because of the differential NMDAR components at synapses onto pyramidal cells and FS PV neurons, NMDAR antagonists acting locally appear unlikely to produce FS neuron-mediated disinhibition. However, it is important to consider the fact that voltage-dependent Mg^{2+} block would mostly prevent the effect of long-lasting NMDAR currents on postsynaptic integration, especially in PV neurons in which NMDAR-mediated currents are more sensitive to Mg^{2+} block than in excitatory cells (Hull et al., 2009). Importantly, it is possible that in certain conditions Mg^{2+} block may be decreased, for example, by transient post-translational modifications including phosphorylation by protein kinase C (Chen and Mae Huang, 1992). Furthermore, during high levels of network activity *in vivo*, membrane depolarization may be sufficient to significantly reduce Mg^{2+} block. An important question is whether relief from Mg^{2+} block by *in vivo* levels of depolarization or by neuromodulation is preferentially observed or more pronounced in PV neurons or in pyramidal cells.

Nevertheless, in support of the idea that NMDAR antagonists are unlikely to produce FS neuron-mediated disinhibition, disynaptic inhibitory postsynaptic potential (IPSP) recruitment is NMDAR-independent in somatosensory cortex (Ling and Benardo, 1995; Hull et al., 2009) and PFC (Rotaru et al., 2011), although it is NMDAR-dependent in hippocampal circuits (Ling and Benardo, 1995; Grunze et al., 1996). NMDAR-dependent disynaptic inhibition may be produced by NFS/PV-negative neurons, which have synapses with strong NMDAR contribution (Lamsa et al., 2007; Lu et al., 2007; Wang and Gao, 2009). NFS neurons, including those in PFC, indeed elicit disynaptic IPSPs, but it has not been determined whether these are NMDAR-dependent (Kapfer et al., 2007; Silberberg and Markram, 2007; Berger et al., 2009).

As mentioned above, a well-established role of NMDARs is to mediate long-term changes in synaptic strength at glutamate synapses onto pyramidal cells, in which multiple forms of NMDAR-dependent long-term synaptic potentiation or depression are observed (Malinow and Malenka, 2002). Interestingly, additional empirical evidence suggesting a weaker NMDAR contribution in synapses onto FS PV neurons compared with pyramidal cells comes from studies of long-term changes in synaptic strength at glutamate synapses onto interneurons. Such studies showed that, consistent with weak calcium influx through NMDARs, long-term potentiation at glutamate synapses onto FS PV neurons is NMDAR-independent (Lamsa et al., 2007; Livet et al., 2007; Sarihi et al., 2008; Nissen et al., 2010; Sambandan et al., 2010), even though the same stimulation protocols produce NMDAR-dependent long-term potentiation in pyramidal cells (Sarihi et al., 2008). Furthermore, in FS PV cells long-term potentiation is enhanced by PV neuron hyperpolarization, which increases NMDAR channel Mg^{2+} block but enhances calcium influx *via* GluA2-lacking AMPARs (Kullmann and Lamsa, 2011). GluA2-lacking AMPARs are an AMPA receptor subtype with atypically high permeability to Ca^{2+} (Man, 2011). Therefore, the findings of NMDAR-independent synaptic plasticity in FS neurons are consistent with a weak NMDAR contribution at their glutamate synapses.

A weaker NMDAR contribution in synapses onto PV cells may be explained by the low density of NMDARs in glutamate synapses onto PV cells compared with pyramidal neurons as shown by electron microscopy studies (Nyiri et al., 2003). Additionally,Hull et al. (2009) provided direct measurements demonstrating that the level of Mg^{2+} block of NMDARs is stronger in FS cells than in pyramidal neurons. This stronger Mg^{2+} block can result from NMDARs that predominantly contain NR2A subunits (Kinney et al., 2006) at the glutamatergic synapses onto FS cells. Among the NR2 subunits, the NR2A subtype produces the fastest NMDA EPSC decay (Dingledine et al., 1999; Cull-Candy and

Leszkiewicz, 2004) and determines strong Mg^{2+} block. In addition, 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 (Yuste et al., 1999; Goldberg et al., 2003a,b; Grunditz et al., 2008). Furthermore, synaptically evoked calcium transients in PV cells are short-lasting and sensitive to blockers of the GluA2 subunit-lacking calcium-permeable AMPARs (Goldberg et al., 2003a). All of these findings lead to the conclusion that the contribution of synaptic NMDARs is low in FS cells, and thus that NMDAR antagonists have limited potential to alter the functionality of these cells. Nevertheless, although present in low number at glutamatergic synapses onto FS cells, it is possible that NMDARs on PV cells are more sensitive to NMDAR antagonists than those present at glutamatergic inputs onto pyramidal cells due to differences in their subunit composition. Although some NMDAR antagonists distinguish among NMDAR subtypes (for instance, the NR2B-selective antagonist ifenprodil), none of these have been used to model NMDAR hypofunction. Additionally, detailed assessments of the specific NMDA subunit composition at the excitatory synapses onto FS cells is currently lacking.

To determine the importance of different glutamate receptor subtypes in PV neurons for the mechanisms of gamma oscillations, we recently compared the effects of fast AMPAR-mediated vs. slow NMDAR-mediated excitation of FS neurons on gamma oscillations production in a computational network model (Rotaru et al., 2011). We found that AMPAR-mediated FS neuron excitation was sufficient to support gamma oscillations, consistent with experiments showing that AMPAR blockade and AMPAR deficiency in PV neurons, but not NMDAR blockade, strongly attenuate gamma oscillations (Traub et al., 1996; Buhl et al., 1998; Fisahn et al., 1998; LeBeau et al., 2002; Cunningham et al., 2006; Fuchs et al., 2007; Roopun et al., 2008). Conversely, decreases in the slow NMDA conductance at pyramidal-FS neuron model synapses increased gamma power in the network model. Similarly, NMDAR antagonists enhance gamma power in animal models (Pinault, 2008; Roopun et al., 2008; Hakami et al., 2009; Pietersen et al., 2009) or human subjects (Hong et al., 2009). Our simulations therefore suggest that rapid FS neuron activation (Jonas et al., 2004; Hu et al., 2010) is crucial for the production of gamma oscillations. Two recent studies (Carlen et al., 2011; Korotkova et al., 2011) showed that genetic deletion of NMDAR selectively from PV positive interneurons increase the power of gamma oscillation in cortex and hippocampus, as predicted by our computational modeling.

The NMDAR contribution to FS PV neuron excitation changes during postnatal development

Because there is a close temporal coincidence between the clinical appearance of schizophrenia and adolescence (Hafner et al., 1991; Walker et al., 1994; Klosterkotter et al., 2001; Reichenberg et al., 2010), it is thought that disturbed maturation of the adolescent brain is crucially involved in the pathophysiology of schizophrenia (Feinberg, 1982; Weinberger, 1987; Keshavan et al., 1994; Uhlhaas and Singer, 2011). Importantly, significant developmental changes during adolescence have been demonstrated for cortical GABAergic neurotransmission (Hoftman and Lewis, 2011). Development of innervation by PV neurons, which sculpts inhibitory networks throughout childhood and adolescence, is dependent on GAD67 levels and activity in rodents (Chattopadhyaya et al., 2007). Environmental insults affecting the development of this inhibitory network, for example, by affecting GAD67 expression, may lead to the abnormal formation of synaptic contacts by these interneurons.

In a strain of genetically modified mice generated recently, NMDARs can be deleted selectively in GABA neurons, including PV cells (Belforte et al., 2010). NMDAR deletion in these mice failed to produce significant effects unless the deletion was induced during

early development, in which case adult mice developed schizophrenia-like behavioral alterations (Belforte et al., 2010). Interestingly, excitatory inputs onto immature PV neurons have strong NMDAR currents that progressively weaken with age, becoming small or absent in adult PV neurons (Wang and Gao, 2009, 2010). Similarly, in the cortex of adult human subjects, 70 % of the PV-positive neurons have undetectable levels of NMDAR subunit mRNA (Bitanihirwe et al., 2009). Because NMDARs are essential for the maturation of excitatory synapses (Waites et al., 2005), NMDAR subunit deletion early in development may persistently affect behavior into adulthood (Belforte et al., 2010) by disrupting the maturation of FS cell connectivity, whereas NMDAR deletion engineered to occur in the mature brain, when NMDAR levels in PV are already significantly decreased, has undetectable effects. Therefore, the results of recent studies suggest that hypofunction of NMDARs onto PV neurons during early development may significantly contribute to cortical circuit alterations in the brain of subjects with schizophrenia (Nakazawa et al., 2011). Importantly, it must be noted that the NMDAR hypofunction hypothesis of schizophrenia is primarily based on observing the effects of NMDAR antagonists administered to adult animals or adult human subjects (Javitt and Zukin, 1991). Therefore, the results of recent studies (Wang and Gao, 2009; Belforte et al., 2010; Rotaru et al., 2011) suggest that NMDAR hypofunction may have substantially different targets when induced in the adult state vs. early development, including adolescence. Specifically, it is possible that NMDAR hypofunction during development affects the maturation of PV neuron connectivity, whereas in adulthood NMDAR hypofunction may affect PFC function by acting at glutamate synapses different from those mediating the activation of FS/PV-positive cells, potentially synapses onto other GABA neuron subtypes or pyramidal cells.

Conclusion

FS neurons display a remarkably fast synaptic activation (Hu et al., 2010), which require short-lasting EPSCs, and thus a weak NMDAR contribution. Moreover, in the cortex of adult mice, the level of NMDAR onto PV cells is significantly lower compared with pyramidal cells leaving small room for NMDAR antagonists to strongly affect PV cell functionality (Rotaru et al., 2011). Importantly, systemic NMDAR antagonist administration increases PFC pyramidal cell firing, possibly by producing disinhibition (Homayoun and Moghaddam, 2007) and repeated NMDA antagonism produces changes in GABA neuron markers that resemble those observed in schizophrenia (Cochran et al., 2002; Rujescu et al., 2006; Behrens et al., 2007, 2008; Morrow et al., 2007). The studies reviewed here lead us to conclude that NMDAR antagonists may produce cortical disinhibition and GABA neuron alterations *via* NMDAR receptors at synaptic sites different from the glutamatergic synapses on PV neurons in the mature cortex. Further studies are clearly necessary to identify the cell types and synaptic mechanisms that may be the target of NMDAR hypofunction in both mature and developing cortical circuits.

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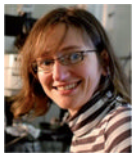
Biographies



Diana Rotaru obtained her MD in 1999, from the University of Medicine and Pharmacy, Timisoara Romania. After a brief clinical internship, between 2000 and 2001, at the Psychiatry Clinic in Timisoara, she continued her postgraduate training in neuroscience between 2002 and 2008, at the University of Pittsburgh, USA, where she studied the properties of inhibitory neurotransmission in prefrontal cortex. Since 2008, she has been a postdoctoral fellow in the Center for Neurogenomics and Cognitive Research, at Vrije University in Amsterdam, Netherlands focusing her research on the role of glutamatergic receptors in learning and memory. The main purpose of her studies is to understand how synaptic transmission contributes to the performance of different cognitive tasks.

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