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Altered Cortical GABA Neurotransmission in Schizophrenia: Insights into Novel Therapeutic Strategies

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Abstract

Altered markers of cortical GABA neurotransmission are among the most consistently observed abnormalities in postmortem studies of schizophrenia. The altered markers are particularly evident between the chandelier class of GABA neurons and their synaptic targets, the axon initial segment (AIS) of pyramidal neurons. For example, in the dorsolateral prefrontal cortex of subjects with schizophrenia immunoreactivity for the GABA membrane transporter is decreased in presynaptic chandelier neuron axon terminals, whereas immunoreactivity for the GABA_A receptor $\alpha 2$ subunit is increased in postsynaptic AIS. Both of these molecular changes appear to be compensatory responses to a presynaptic deficit in GABA synthesis, and thus could represent targets for novel therapeutic strategies intended to augment the brain's own compensatory mechanisms. Recent findings that GABA inputs from neocortical chandelier neurons can be powerfully excitatory provide new ideas about the role of these neurons in the pathophysiology of cortical dysfunction in schizophrenia, and consequently in the design of pharmacological interventions.

Keywords

chandelier neuron; basket neuron; parvalbumin; GABA-A receptor; prefrontal cortex

The clinical features of schizophrenia include both psychosis and cognitive impairments [1]. The psychotic features, including abnormal perceptual experiences, delusions, disorganized thinking, and bizarre behaviors, are frequently the most striking clinical manifestations of the illness; although intensely disturbing, psychotic symptoms typically respond, at least in part, to currently available antipsychotic medications [2]. The cognitive impairments encompass a number of domains, including semantic and explicit memory, attention, working memory, and executive function, appear to be the core features of the illness; and are not a consequence of pharmacological treatments or illness chronicity [3]. For example, cognitive abnormalities are present in most individuals with schizophrenia; are evident well before the first episode of psychosis or administration of medications; and occur in a milder form in unaffected relatives of individuals with schizophrenia, suggesting that they reflect the genetic risk for the illness [4]. Furthermore, the degree of cognitive impairment is the best predictor of long-term functional outcome in schizophrenia [5]. In contrast with psychosis, the cognitive deficits of schizophrenia show little to no improvement with existing pharmacological treatments; consequently, finding novel molecular targets to improve cognition has become a major focus of current schizophrenia research [2].

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Working memory, the ability to transiently maintain and manipulate a limited amount of information in order to guide thought or behavior, has been shown consistently to be impaired in schizophrenia [6,7], and this impairment is accompanied by altered activation of the dorsolateral prefrontal cortex (DLPFC) [8,9]. Altered DLPFC activity during working memory tasks appears to be relatively specific to the disease process of schizophrenia because these disturbances are present in medication-naïve individuals with schizophrenia, but are absent (or seen only to a milder degree) in subjects with other psychotic disorders or major depression [10,11]. Furthermore, children diagnosed with schizophrenia as adults exhibit a developmental lag in the maturation of working memory function, whereas children who later developed recurrent depression do not have similar premorbid cognitive disturbances [12].

Altered markers of cortical GABA neurotransmission in schizophrenia

Substantial evidence indicates that cortical GABA neurotransmission is altered in schizophrenia. Early postmortem studies of schizophrenia revealed evidence of decreased GABA synthesis [13] and uptake [14], and increased binding to GABA-A receptors in the neocortex [15,16]. Multiple studies conducted over the past 15 years by a number of research groups, using different techniques and cohorts of subjects, have consistently found reduced levels of the transcript for the 67 kilodalton isoform of glutamic acid decarboxylase (GAD67), the enzyme responsible for most GABA synthesis [17,18], in the DLPFC of subjects with schizophrenia [19–29]. Despite the consistent finding of lower mean GAD67 mRNA levels in subjects with schizophrenia, the variability in GAD67 mRNA levels across schizophrenia subjects suggests the possibility of different subtypes of schizophrenia, with a large proportion of subjects having low GAD67 expression, but with smaller subgroups characterized by normal, or perhaps even elevated, levels of GAD67. Importantly, in the two studies conducted to date, lower GAD67 mRNA levels were accompanied by lower GAD67 protein levels [21,30], consistent with the idea that the capacity to synthesize cortical GABA is reduced in schizophrenia.

The deficit in cortical GAD67 mRNA expression in schizophrenia is not restricted to the DLPFC. For example, similar reductions in GAD67 mRNA were found in the DLPFC, anterior cingulate cortex, primary motor cortex and primary visual cortex from the same subjects with schizophrenia [26], suggesting that GABA synthesis is altered in a similar manner across neocortical regions that markedly differ in structures, connectivity and function. Furthermore, lower levels of GAD67 mRNA were reported in orbital frontal, superior temporal and anterior cingulate cortices in other subject cohorts [31–33]. Thus, disturbances in GABA neurotransmission could represent a common pathophysiology for different domains of cortical dysfunction in schizophrenia, raising the possibility that pharmacological agents with the appropriate specificity for certain GABA-related targets might be effective for a range of cognitive and sensory abnormalities in schizophrenia.

At the cellular level, the expression of GAD67 mRNA was not detectable in ~25–35% of GABA neurons in layers 2–5 of the DLPFC of subjects with schizophrenia, but the remaining GABA neurons exhibited normal levels of GAD67 mRNA [19,20]. Furthermore, levels of the mRNA for the GABA membrane transporter (GAT1), a protein mediating the reuptake of released GABA into nerve terminals, was also decreased [34] in a similar minority of GABA neurons [35]. These findings suggest that both the synthesis and re-uptake of GABA are lower in a subset of DLPFC interneurons in schizophrenia.

Alterations in parvalbumin-containing GABA neurons in schizophrenia

Subclasses of cortical GABA neurons differ in a number of molecular, electrophysiological and anatomical properties [36]. For example, the calcium-binding proteins, parvalbumin

(PV) and calretinin, and the neuropeptide somatostatin are, with a few exceptions, expressed in separate populations of GABA neurons in the primate neocortex [37–39]. In the monkey DLPFC, these subtypes exhibit different membrane firing properties and their axons have different arborization patterns and synaptic targets [40–42]. For example, the axon terminals of PV-containing chandelier and basket neurons principally target the axon initial segments (AIS) and cell body/proximal dendrites, respectively, of pyramidal neurons [43,44], the calretinin-containing double-bouquet cells tend to synapse on the dendrites of other GABA cells [45], and the somatostatin-containing Martinotti cells innervate the distal dendrites of pyramidal neurons [46–48].

The affected GABA neurons in schizophrenia include the PV-positive neurons which comprise ~25% of GABA neurons in the primate DLPFC. For example, in individuals with schizophrenia, the expression level of PV mRNA is reduced in layers 3–4 of the DLPFC, and ~50% of PV mRNA-containing neurons in these layers lack detectable levels of GAD67 mRNA [49]. In contrast, the ~50% of GABA neurons in the primate DLPFC that express calretinin appear to be unaffected in schizophrenia [49].

The alterations in PV mRNA expression in schizophrenia appear to reflect deficits in gene expression per neuron, and not a reduced number of PV neurons [49]. Consistent with this finding, the density of PV-immunoreactive neurons, as visualized by immunocytochemistry, was not altered in either DLPFC areas 9 or 46 in schizophrenia [50,51]. Other studies reported fewer PV-positive neurons in these areas due to primarily to lower densities of labeled neurons in layers 3–5 [52–54]. The apparent disparity in these results might be attributable to differences in tissue processing methods. For example, the studies that did not find a difference in density of PV-immunoreactive neurons utilized paraformaldehyde-fixed, free-floating tissue sections that maximize tissue penetration of the antibody, whereas the studies that reported lower neuronal density employed paraffin-embedded sections, which are typically associated with lower immunoreactivity. Interestingly, the reduction in PV neuron density in the latter studies was detected in layers 3–5, the layers where the largest reduction in PV mRNA in schizophrenia was found [49]. Thus, lower PV mRNA expression per neuron in schizophrenia in combination with a reduced capacity to detect PV protein due to paraffin embedding could have resulted in the *appearance* of a lower density of PV neurons in schizophrenia in some studies [52–54]. Together, these findings suggest that lower levels of PV protein in schizophrenia make these neurons more difficult to visualize with immunocytochemical techniques, but that the number of PV neurons is not altered in the illness, consistent with the findings that the total number of Nissl-stained neurons in the frontal cortex does not differ between subjects with schizophrenia and normal comparison subjects [19,55].

Alterations in the chandelier class of PV neurons in schizophrenia

The axons of chandelier (or axo-axonic) cells arborize extensively in the vicinity of the cell body, with each branch ending in a vertical array of closely-spaced axon terminals. The terminals from one or more chandelier cells synapse exclusively onto the axon initial segment (AIS) of a pyramidal neuron, outlining the AIS in a distinctive arrangement known as a “cartridge” [56]. In turn, the innervation of the AIS arises exclusively from chandelier cells [57,58]. The axon cartridges of chandelier neurons contain high levels of the GABA membrane transporter (GAT1), the protein that terminates GABA action at the synapse by reuptake into the nerve terminals. In the DLPFC of subjects with schizophrenia, GAT1 immunoreactivity appears to be preferentially reduced in the cartridges of PV-containing chandelier neurons [59,60]. In the postsynaptic targets of these axon cartridges, the AIS of pyramidal neurons, immunoreactivity for the GABA-A receptor $\alpha 2$ subunit (which is present in most GABA-A receptors located in AIS [61]) is markedly increased in

schizophrenia [62]. These changes appear to be specific to the disease process of schizophrenia because they are not found in subjects with other psychiatric disorders or in monkeys exposed chronically to antipsychotic medications [20,35,49,62].

The pre- and postsynaptic changes in GAT1 and GABA-A receptor α_2 subunit immunoreactivity are inversely correlated [62], suggesting that they index the degree of alteration in GABA neurotransmission at the chandelier cell inputs to pyramidal neurons. Consistent with this interpretation, several lines of evidence suggest that the reductions in pre-synaptic GABA markers (GAT1 and PV) and increased post-synaptic GABA-A receptors could be compensatory responses to a deficit in GABA release from chandelier neurons. First, PV is a slow calcium buffer that accelerates the decay of Ca^{2+} transients in GABA nerve terminals following action potentials [63,64]. Thus, PV decreases the residual Ca^{2+} levels that normally accumulate in axon terminals and enhance GABA release during repetitive firing [63]. Genetically-engineered reductions of PV in mice increase residual Ca^{2+} and synaptic facilitation [63,65], consistent with the idea that lower PV expression in schizophrenia could serve to augment GABA release from neurons with deficient GABA synthesis. Second, because the blockade of GABA re-uptake via GAT1 prolongs the duration of IPSCs when synapses located close to each other are activated synchronously [66], lower levels of GAT1 in chandelier neuron cartridges in schizophrenia would be expected to prolong IPSCs and increase the probability of IPSC summation, and thus the efficacy of IPSC trains. Third, the up-regulation of the post-synaptic GABA-A receptors that contain α_2 subunits would increase the efficacy of the GABA that is released from chandelier neuron cartridges. Thus, the combined reduction of PV and GAT1 proteins in chandelier cell axon cartridges, and the up-regulation of post-synaptic GABA-A receptors, would act synergistically to increase the efficacy of GABA neurotransmission at pyramidal neuron AIS during the types of repetitive neuronal activity associated with working memory. Although the persistence of cognitive impairments in individuals with schizophrenia suggests that these compensatory changes in GABA neurotransmission from chandelier neurons are insufficient to restore normal function, they do suggest that augmenting these responses might represent a novel therapeutic strategy for the treatment of cortical dysfunction in schizophrenia. Of course, these compensatory responses might be maximized in some individuals with schizophrenia, and thus not amenable to augmentation.

GABA-based therapies for cognitive impairments in schizophrenia

The findings summarized above suggest several possibilities for novel therapeutic strategies in schizophrenia that focus on augmenting the brain's own compensatory mechanisms. For example, GAT1 inhibitors might be considered. However, this approach has at least two theoretical shortcomings. First, GAT1 immunoreactivity appears to be selectively lower in the axon terminals of chandelier neurons [59]. Thus, GAT1 inhibition is likely to alter GABA neurotransmission at synapses that are not abnormal in schizophrenia, perhaps producing unintended adverse effects on cortical function. Second, the levels of GAT1 protein are markedly reduced in chandelier neuron cartridges in schizophrenia, suggesting that the compensatory response is already at a maximum and not amenable to additional pharmacological intervention [67].

Alternatively, agents with selective agonist activity at GABA-A receptors containing the α_2 subunit may, by further enhancing an intrinsic compensatory mechanism selectively at the affected synapses, help restore normal pyramidal neuron activity and thereby improve DLPFC functional output and working memory function in schizophrenia. In particular, treatment with benzodiazepine-like agents selective for the GABA-A receptor α_2 subunit would increase the frequency of GABA-A receptor openings, enhancing chloride ion flow at pyramidal cell AIS. Furthermore, benzodiazepine-like agents enhance IPSPs only in the presence of GABA and do not independently activate GABA-A receptors. Thus, treatment

with an α_2 subunit-selective benzodiazepine, in the context of subnormal endogenous GABA activity, may help maintain the appropriate coordination of pyramidal neuron activity provided by chandelier cell firing. Indeed, since the relative number of putative chandelier cells (as assessed by counts of PV mRNA- or protein-containing neurons) does not appear to be reduced in the DLPFC in schizophrenia [49,50,52], it seems likely that some level of GABA input to pyramidal neuron AIS persists in the illness. In contrast, direct agonists capable of independently activating GABA-A α_2 receptors are unlikely to incorporate the critical timing of inhibition provided by the intrinsic firing of chandelier cells. The specificity of drug actions for dysfunctional GABA synapses may also be enhanced by the up-regulated state of the GABA-A α_2 receptors at the AIS in schizophrenia. In particular, it may be possible to devise dosing strategies that would activate these receptors while leaving synaptic sites with normal levels of GABA-A α_2 receptors relatively unaffected. Furthermore, given the anxiolytic effects mediated by GABA-A α_2 containing receptors, such agents may not only improve cognitive function, but also reduce the types of stress responses that appear to be associated with the exacerbation of psychosis in schizophrenia [68].

Consistent with these ideas, a novel compound that enhances GABA neurotransmission at GABA-A receptors containing α_2 subunits (MK-0777, provided by Merck) was associated with improved performance on three working memory tasks in subjects with schizophrenia [69] and in an animal model of the cognitive deficits of schizophrenia [70] in proof-of-concept studies. In addition, in normal subjects this medication did not have the cognitive-impairing effects seen with available benzodiazepines that activate GABA-A receptors with α_1 , α_2 , α_3 or α_5 subunits [71].

Is the output of chandelier neurons excitatory in the neocortex?

Chandelier neurons have been considered to be powerful inhibitors of pyramidal cell output, exercising “veto power” by virtue of the close proximity of their synaptic inputs to the site of action potential generation in pyramidal neurons. In the adult brain, high expression of the potassium-chloride co-transporter (KCC2) results in the extrusion of chloride from the cell [72]. Thus, when GABA-A receptors are activated, chloride ions flow into the cell along a concentration gradient, resulting in hyperpolarization of the membrane, and a reduced probability of cell firing. However, due to apparent absence of KCC2 in the AIS of neocortical pyramidal neurons, the release of GABA from chandelier neuron axon terminals in an *in vitro* slice preparation was found to powerfully depolarize pyramidal cells, frequently to the point of firing an action potential [73]. This excitation of pyramidal cells by chandelier cells was replicated in both rodent and human neocortex [74,75]. Studies using recording techniques that were able to exclude potential methodological confounds showed that both basket and chandelier neurons are inhibitory in the hippocampus [76], but that neocortical chandelier cells are able to produce GABA-mediated excitation [77].

Chandelier neurons and the pathophysiology of schizophrenia

Prevailing views of the role of chandelier neurons in the pathophysiology of schizophrenia are based on the idea that chandelier neurons potently inhibit pyramidal cells, and the presumed deficit of GABA in these neurons contributes to impaired synchronization of network activity in postsynaptic pyramidal cells [78]. However, the idea that chandelier cell inputs can be excitatory suggests alternative considerations. For example, if chandelier cell inputs to pyramidal neurons are usually depolarizing, then reduced synthesis of GABA in these neurons could result in a marked decrease in the excitatory output of pyramidal neurons. It is also important to note that although GAD67 mRNA is markedly reduced in ~50% of PV neurons in the DLPFC of subjects with schizophrenia [49], it has not been

directly shown that chandelier cells are among the affected cells, in the same way that the alterations in GAT1 and GABA-A $\alpha 2$ immunoreactivities have been shown in presynaptic chandelier cartridges and post-synaptic pyramidal cell AIS. Thus, it is possible that the alterations in pre- and post-synaptic markers of chandelier cell inputs to pyramidal neurons in schizophrenia reflect a compensatory response to increase excitatory drive to pyramidal neurons that lack normal levels of excitation due to an intrinsic deficit in dendritic spines, the primary site of excitatory inputs [79]. That is, lower levels of PV and GAT1 in chandelier neuron axon terminals, and increased post-synaptic $\alpha 2$ -containing GABA-A receptors, would all serve to increase GABA-mediated depolarization at pyramidal neuron AIS. Thus, the observed changes in chandelier neurons in schizophrenia could reflect homeostatic responses to preserve activity in the neural networks formed by DLPFC pyramidal neurons in the face of a disease-related deficiency in the capacity of these neurons to receive excitatory drive from other pyramidal cells [80].

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