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Perisomatic Inhibition and Cortical Circuit Dysfunction in Schizophrenia

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Although psychosis (e.g., hallucinations and delusions) is the most striking clinical feature of schizophrenia, multiple lines of evidence indicate that impairments in cognition represent the core of the illness, as these deficits are present and progressive years before the onset of psychosis[1]. The cognitive deficits span multiple domains, suggesting that they reflect an overarching alteration in cognitive control, the ability to adjust thoughts or behaviors in order to achieve goals[2]. Cognitive control depends on the coordinated activity of a number of brain regions, including the dorsolateral prefrontal cortex (DLPFC). Subjects with schizophrenia exhibit altered activation of the DLPFC[3], and reduced frontal lobe gamma band (30–80 Hz) oscillations, while performing tasks that require cognitive control[4;5].

Because gamma oscillations require strong and fast inhibition from GABA neurons[6], alterations in DLPFC GABA neurotransmission have been hypothesized to contribute to altered gamma oscillations and impaired cognition in schizophrenia[7]. For example, administration of iomazenil, an inverse agonist at the benzodiazepine site of $GABA_A$ receptors that negatively modulates GABA neurotransmission, exacerbates symptoms in subjects with schizophrenia at doses that do not affect healthy controls[8]. Consistent with this interpretation, manipulations in animal models that reduce GABA-mediated inhibition diminish gamma oscillations[9] and impair cognitive function[10;11]. In contrast, treatment with a positive allosteric modulator of $GABA_A$ receptors was associated with increased frontal lobe gamma oscillations during a cognitive control task in subjects with schizophrenia[12].

The cellular basis for altered GABA neurotransmission in schizophrenia appears to include a presynaptic deficit in GABA synthesis. For example, although cortical expression of the 65 kD isoform of glutamic acid decarboxylase (GAD65) appears to be normal or only modestly altered in schizophrenia[13;14], transcript levels of GAD67, which is responsible for most GABA synthesis in the cortex[15], have been consistently found to be lower in the DLPFC of subjects with schizophrenia[16]. Lower levels of GAD67 mRNA are particularly prominent in the subclass of GABA neurons that express the calcium-binding protein parvalbumin (PV)[17]. Importantly, in vivo studies using optogenetic techniques have demonstrated that PV neuron activity is essential for driving cortical gamma oscillations[18;19].

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Role of PV basket neurons in gamma oscillations

Cortical PV-containing GABA neurons consist of two major types: chandelier or axoaxonic cells which innervate the axon initial segment (AIS) of pyramidal neurons, and basket cells which innervate the cell body and proximal dendrites and spines of pyramidal neurons[20–22]. The location of these inputs onto the perisomatic membrane compartment indicates that both cell types are capable of activating relatively large $GABA_A$ receptor conductances near the site of action potential initiation in the AIS of pyramidal neurons. Because the strength of synaptic $GABA_A$ receptor conductance is determined by its proximity to the site of spike initiation[23], chandelier cells would be predicted to have the strongest inhibitory power.

However, synaptic inputs from neocortical chandelier cells actually appears to be excitatory, as stimulation of these cells can initiate spikes in postsynaptic pyramidal cells[24]. This excitatory effect may be due to much lower levels of the chloride transporter KCC2, which extrudes chloride, at the AIS relative to the soma or dendrites[24;25]. The resulting higher intracellular levels of chloride in the AIS would lead to a depolarizing postsynaptic $GABA_A$ receptor current[26]. Indeed, under experimental conditions that preserve the physiological intracellular chloride concentration, chandelier cell inputs depolarize postsynaptic pyramidal neurons, whereas inputs from PV-containing basket cells are hyperpolarizing[24;27], consistent with higher levels of KCC2 transporters in the somatic membrane[24;25]. In contrast, paired recording experiments in the hippocampus have demonstrated that inputs from both chandelier and basket neurons hyperpolarize pyramidal neurons[28], even though low levels of KCC2 are found at the AIS membrane of hippocampal pyramidal cells[25]. Understanding and reconciling these differences in the functional properties of chandelier cell inputs[29] is critical to determining how alterations in these neurons contribute to cortical circuit dysfunction in schizophrenia[30].

Important functional differences among PV-containing chandelier and basket neurons, and the class of basket neurons that express the cannabinoid receptor 1 (CB1R) and the neuropeptide cholecystokinin (CCK)[31], are suggested by findings that the relative levels of GAD67 and GAD65 proteins in axon terminals differ substantially across these cell types[32]. The GAD67/GAD65 ratio is ~1.5 in the axon terminals of PV-containing basket cells, but the ratio is very high (> 15) in chandelier cell axon terminals and very low (< 0.2) in the axon terminals of CB1R basket cells[32] (Figure 1). These cell type-specific differences are likely to have important functional implications given the existing data on the nature of the contributions of GAD67 and GAD65 to GABA synthesis. For example, deletion of the GAD67 gene in mice is lethal and is associated with ~90% reduction of brain GABA levels[33;34]. Consistent with these observations, mice with GAD67 deficiency restricted to the cerebellum have very weak $GABA_A$ receptor-mediated transmission even at low stimulus frequency[35]. In contrast, mice with deletion of the GAD65 gene survive into adulthood, have only a ~ 20% reduction in total brain GABA concentration[36], and exhibit normal $GABA_A$ receptor-mediated synaptic transmission during low frequency stimulation, but have markedly impaired transmission at stimulation frequencies >30 Hz[37;38]. Together, these findings suggest an essential role for GAD67 in baseline GABA synthesis and synaptic transmission, with GAD65 contributing to GABA synthesis principally under conditions of high frequency firing. Thus, at least in the primate DLPFC, the GAD67/65 ratio in PV basket cell terminals might equip these cells with a greater capacity, relative to chandelier neurons, for the type of repetitive neurotransmitter release required for gamma oscillations.

The kinetics of GABA neurotransmission, as determined by the type of post-synaptic GABAA receptor, may also favor an essential role for PV basket cells in gamma oscillations. That is, the $GABA_A$ receptor-mediated inputs involved in gamma

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synchronization must inhibit postsynaptic neurons for a length of time compatible with the gamma oscillation period. The $GABA_A$ receptor current duration depends on the subunit composition of the receptor[26;39], with $GABA_A$ receptors containing α1 subunits producing currents with a faster decay than those containing other α subunits[40]. The inputs from PV basket cells are principally mediated by α1-containing receptors, whereas slower α2-containing receptors predominate at both chandelier and CB1R/CCK basket cell inputs[41–45]. Thus, PV basket cells produce IPSCs with the faster current decay required for gamma oscillations. Furthermore, PV basket cell terminals produce a single synchronous GABA release event per presynaptic action potential[46;47] in contrast to the multiple asynchronous release events, which result in long-lasting inhibition, produced by CB1R/CCK basket cells.

The idea that PV basket cells have the unique properties required for gamma band synchrony is further supported by electrophysiological findings that PV basket cell firing is more strongly coupled to the gamma oscillation cycle than is the firing of chandelier neurons or CCK basket cells[48], and the firing of the latter two cell types is strongly coupled to the much slower theta oscillations[49–51]. Furthermore, gamma oscillations are significantly reduced by stimulation of presynaptic opioid receptors that suppress GABA release from PV basket cells but not from chandelier neurons or CCK basket cells[48].

Alterations in prefrontal GABA neurons and gamma oscillations in schizophrenia

The findings reviewed above converge on the conclusion that perisomatic inputs from PV basket cells are the main source of $GABA_A$ receptor-mediated synchronization at gamma frequencies. This interpretation then raises the question of whether and how alterations in PV basket cells in the DLPFC of subjects with schizophrenia could provide the pathological basis for altered frontal lobe gamma oscillations. Because phasic excitation of PV neurons is thought to be required for gamma oscillations in pyramidal-interneuron network models, and their tonic depolarization is implicated in interneuron network models[6,52], the impaired gamma oscillations in schizophrenia could be due to a deficit of glutamate transmission[53]. Indeed, hypofunction of NMDA receptors in PV cells has been suggested to be a core abnormality of the disorder, accounting for the deficits in both GAD67 and PV expression[54–56]. However, experimental data[57] indicate that glutamate synapses onto PV basket cells typically produce excitatory postsynaptic potentials (EPSCs) with a faster decay and weaker NMDA receptor contribution than do those onto pyramidal cells or other types of GABA neurons, suggesting that the rapid synaptic activation of PV basket cells is dependent, at least in part, on their fast AMPA receptor-mediated EPSCs[58]. Similarly, computational modeling studies demonstrated that fast AMPA-mediated excitation of PV basket cells is critical for gamma band synchrony and that including slower decaying NMDA-mediated EPSCs in basket cells disrupts gamma synchrony[57]. Consistent with these observations, NMDA receptor antagonists either enhance or do not affect gamma oscillations, whereas AMPA receptor antagonism completely abolish them[59–62]. Thus, although the effects of NMDA receptor antagonists on gamma oscillations might differ across cortical regions or layers, the observation that in most cases gamma synchrony is unaffected by NMDA receptor blockade[61;63] suggests that the disturbance in PV basket cell function contributing to impaired gamma oscillations in schizophrenia is independent of phasic NMDA receptor activation at synapses onto these cells.

Alternatively, impaired PV basket cell function in schizophrenia might reflect altered GABA synthesis in these neurons. Levels of GAD67 mRNA are markedly lower in ~50% of PV neurons in schizophrenia[17], but in the absence of cell type specific markers, it has not been possible to determine whether this expression deficit is present in chandelier and/or

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basket cells. However, both the density of[64], and levels of GAD67 protein in[65], PV-labeled puncta, presumed to be basket cell terminals, appear to be lower in DLPFC layers 3 and 4 of subjects with schizophrenia. In addition, expression of the $GABA_A$ receptor α1 subunit (and of the β2 subunit with which it preferentially assembles) is also preferentially lower in this laminar location, whereas other $GABA_A$ receptor subunits are either unchanged or show a different laminar pattern of altered expression[66–68] (Figure 2). Thus, both pre- and post-synaptic markers of PV basket cell inputs appear to be lower in layers 3 and 4 of subjects with schizophrenia, suggesting that weaker synaptic transmission from these PV basket cells could contribute to impaired gamma oscillations in the illness.

The strength of the postsynaptic response to GABA depends on the driving force for the influx of chloride through $GABA_A$ receptor channels. Intracellular chloride levels are determined by the balance of activity between the chloride transporters NKCC1 and KCC2 which mediate chloride uptake and extrusion, respectively[26]. Although the expression of these transporters does not appear to be altered in the DLPFC of subjects with schizophrenia, two kinases (OXSR1 and WNK3) that phosphorylate both chloride transporters, decreasing the activity of KCC2 and increasing the activity of NKCC1, are markedly over-expressed in schizophrenia, including in layer 3 pyramidal neurons[69]. If the higher levels of OXSR1 and WNK3 mRNA represent increased kinase activity, then the intracellular chloride concentration would be expected to be greater than normal in schizophrenia (Figure 3), potentially resulting in less hyperpolarization of layer 3 pyramidal neurons when GABA is released from PV basket cells.

Thus, the available data suggest that a number of factors (pre-synaptic reductions in GABA synthesis or the number of axon terminals; post-synaptic reductions in the number of, or chloride ion flow through, $GABA_A$ receptors) might contribute to a reduced capacity of PV basket cells to synchronize pyramidal neurons at gamma frequencies in schizophrenia, and thus might represent a neural substrate for the disease-related impairments in cognitive control. The tendency for at least some of these alterations to be most prominent in layer 3 is consistent with evidence that circuitry in this laminar location of the primate neocortex is critical for both gamma oscillations[70] and for delay-dependent cognitive control tasks[71]. Thus, interventions directed at enhancing the function of layer 3 PV basket cells might prove to be an effective means of improving cognitive control in individuals with schizophrenia.

Highlights

Deficits of cognitive control in schizophrenia are associated with altered gamma oscillations in the prefrontal cortex.

Paralbumin basket interneurons appear to play a central role in generating cortical gamma oscillations.

Pre- and post-synaptic alterations in the strength of inhibitory inputs from parvalbumin basket neurons to pyramidal neurons in the middle layers of the prefrontal cortex may contribute to the neural substrate for impaired gamma oscillations in schizophrenia.

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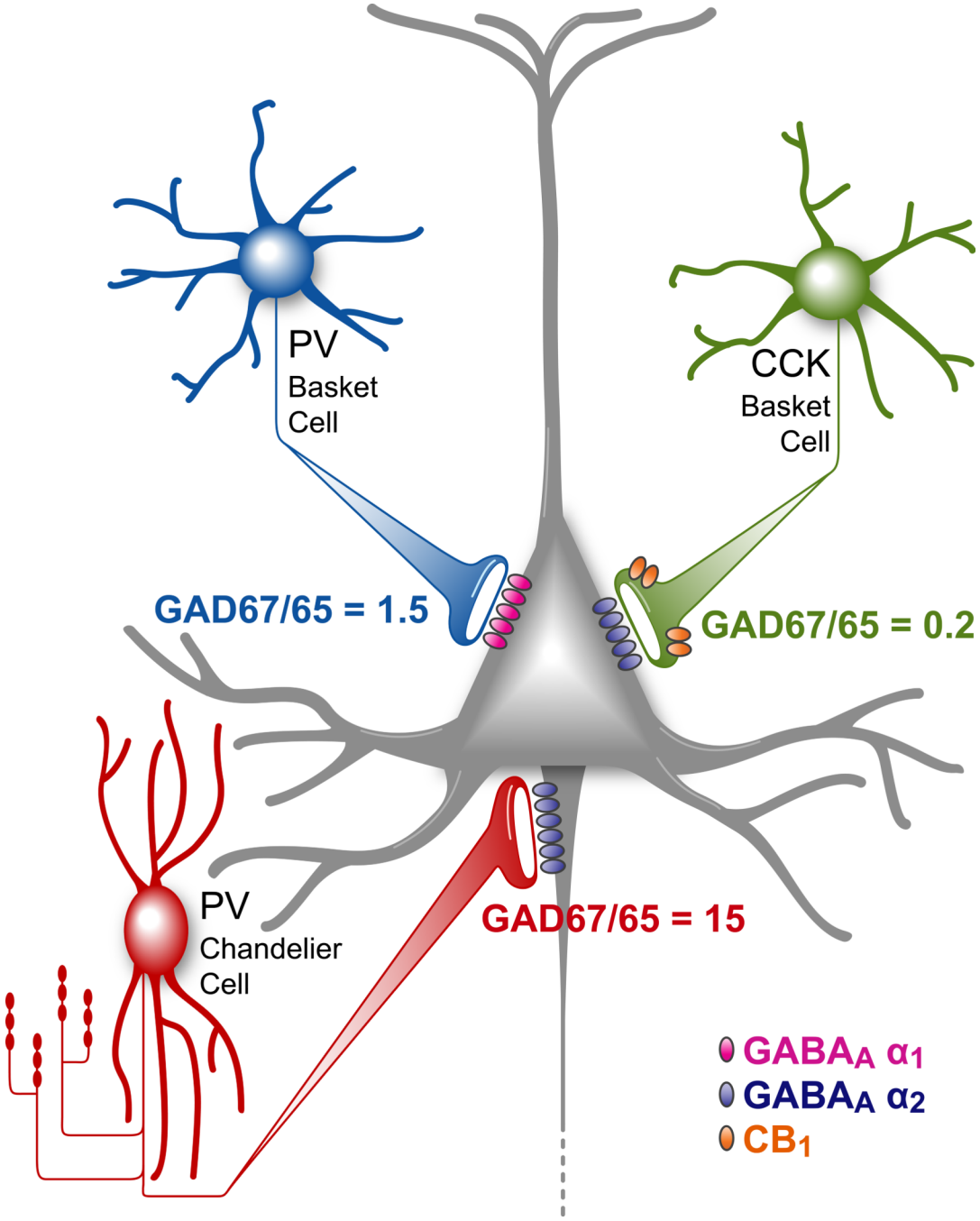

Figure 1.
Schematic summary of the three main types of GABA neurons providing perisomatic inputs to pyramidal neurons and the ratio of the two GABA synthesizing enzymes in the axon terminal levels of each cell type. Adapted from [32].

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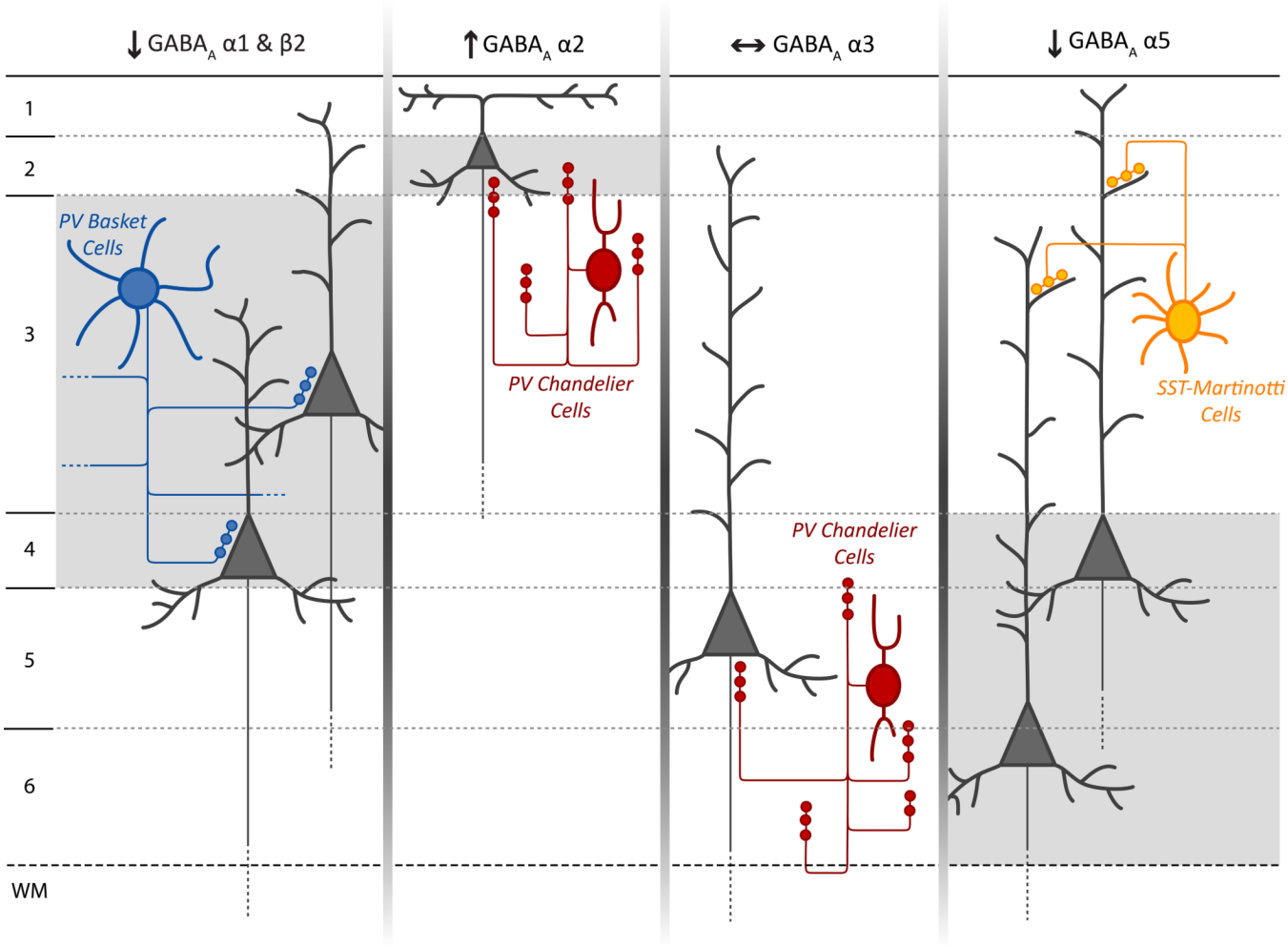

Figure 2.

Schematic summary of layer-specific transcript alterations in postsynaptic $GABA_A$ receptor subunits in the DLPFC of subjects with schizophrenia and their hypothesized relationship to different classes of GABA neurons. For each $GABA_A$ subunit, the background shading marks the cortical layers where the indicated change in expression of that subunit was found. The lower expression of α1 and β2 mRNAs in layers 3 and 4 match that of the presynaptic alterations in PV basket cells. The increase in α2 expression in layer 2 is consistent with previous findings of pre- and post-synaptic alterations in chandelier cell inputs to the axon initial segment of pyramidal cells in this location[7]. In contrast, the absence of alterations in α3 subunit expression, which is present post-synaptic to chandelier cells in pyramidal neurons in layers 5–6, matches the failure to find significant changes in chandelier cell markers in these layers. The lower α5 subunit expression was observed in the deeper layers of the DLPFC where the somata of pyramidal neurons whose apical dendrites are known to be innervated by SST+ Martinotti cells, thought also to be affected in schizophrenia[72;73], are predominantly located. Adapted from [67].

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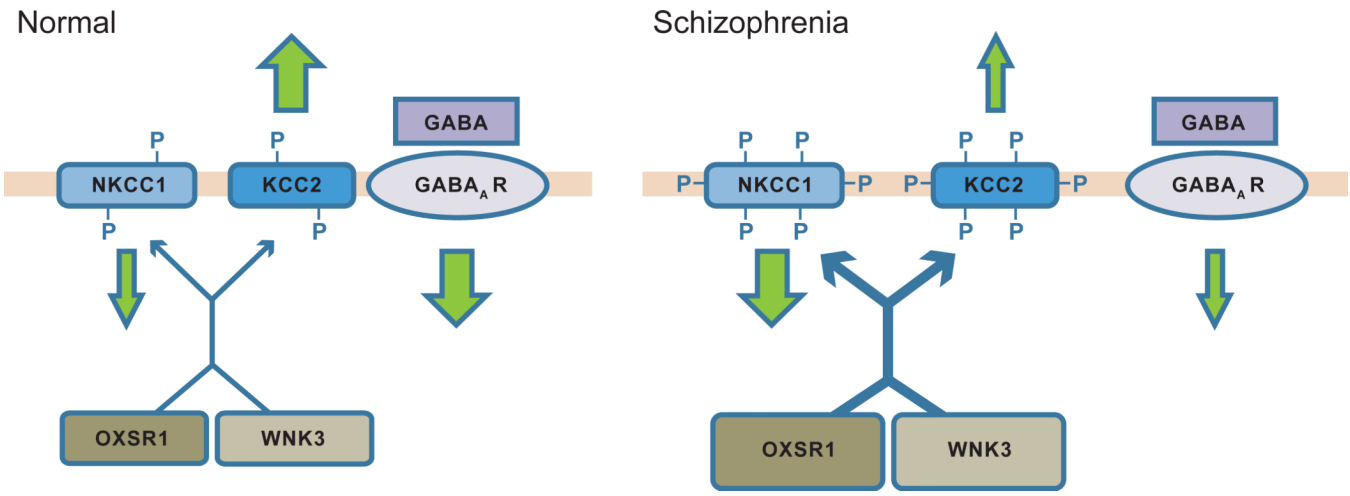

Figure 3.

Hypothesized model of the interactions between chloride (Cl^-) transporters (NKCC1 and KCC2) and two kinases (OXSR1 and WNK3) that regulate their activity via phosphorylation. In both panels, the orange bar represents the cell membrane, with the extracellular domain above and the intracellular domain below the bar. The size and orientation of the green arrows indicates the magnitude and direction of Cl^- ion flow mediated by NKCC1, KCC2 and $GABA_A$ receptor Cl^- channels. (A) In normal adult neurons, intracellular Cl^- concentration is low due to low levels of NKCC1 and high levels of KCC2. The binding of GABA to $GABA_A$ receptors triggers Cl^- entry and membrane hyperpolarization. (B) In schizophrenia, increased OXSR1 and WNK3 kinase levels lead to increased phosphorylation (P) of both chloride transporters and consequently increased NKCC1 activity and decreased KCC2 activity, producing a greater intracellular Cl^- concentration. Thus, when $GABA_A$ receptors are activated, Cl^- influx is reduced and GABA neurotransmission is less hyperpolarizing. Adapted from [69].