Deficient GABAergic gliotransmission: A Possible Cause of Broadening of Sensory Tuning in Schizophrenia

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Abstract— We examined how the depression of intracortical inhibition due to a reduction in ambient GABA concentration impairs perceptual information processing in schizophrenia. A neural network model with a gliotransmission-mediated ambient GABA regulatory mechanism was simulated. In the network, interneuron to glial cell and principal cell to glial cell synaptic contacts were made. The former hyperpolarized glial cells and let their transporters import (remove) GABA from extracellular space, thereby lowering ambient GABA concentration, reducing extrasynaptic GABAa receptor-mediated tonic inhibitory current and thus exciting principal cells. In contrast, the latter depolarized glial cells and let the transporters export GABA into the extracellular space, thereby elevating ambient GABA concentration and thus inhibiting principal cells. A reduction in ambient GABA is assumed in a schizophrenia network. Multiple dynamic cell assemblies were organized as sensory feature columns. Each cell assembly responded to a sensory feature stimulus. Tuning performance of the network to the stimulus was evaluated in relation to the level of ambient GABA. Transporter-deficient glial cells caused a deficit in the GABAergic gliotransmission and reduced ambient GABA concentration, which markedly deteriorated the tuning performance of the network, broadening the sensory tuning. We suggest that a deficit in GABAergic gliotransmission may cause a reduction in ambient GABA concentration, leading to a broadening of sensory tuning in schizophrenia. The GABAergic gliotransmission mechanism, proposed here, may have an important role in the regulation of local ambient GABA levels.

Key Words: Ambient GABA, GABAergic Gliotransmission, Sensory Tuning, Schizophrenia

1 Introduction

Deficits in basic perceptual function have been evidenced in schizophrenia. Rojas and colleagues1) found a significant broadening on auditory tuning (at 1kHz) in patients with schizophrenia. They suggested that the depression of intracortical inhibition between cortical frequency columns might disturb tonotopic mapping and therefore broaden the auditory tuning. It still remains to be seen how deficits in basic perceptual function are caused in schizophrenia.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter, and has been the focus on the research for neuronal mechanism of cognitive deficits in schizophrenia. Experimental studies2, 3) estimated the global GABA level in visual cortex, indicating a reduction in GABA concentration in the schizophrenic group compared to the healthy control group. The researchers investigated a relationship between GABA concentration and orientation-specific surround suppression3), and a relationship between GABA concentration and orientation-tuning3). They found a highly significant positive correlation between these variables, indicating the reduction of ambient GABA levels might lead to the depression of intracortical inhibition and impair perceptual information processing in schizophrenia. One important question remained: What is the underlying neuronal mechanism?

As to the maintenance of ambient GABA levels, Richerson and colleagues4, 5, 6) made an interesting suggestion that a GABA transporter such as GAT-1 might be crucial not only for importing (removing) GABA from but also for exporting it into the extracellular space. Transporter, embedded in plasma membranes of glial cells (and GABAergic interneurons), can clamp ambient GABA at a certain level at rest. Glial cells are thought to be one of the possible sources of GABA responsible for extrasynaptic GABAa receptor-mediated tonic inhibitory current7, 8). Experimental studies9, 10) indicated GAT1-deficient cortical glial cells and interneurons in schizophrenic patients.

The purpose of this study is to elucidate how the depression of intracortical inhibition due to a reduction in ambient GABA concentration impairs perceptual information processing in schizophrenia. To regulate ambient GABA concentration in a neural network, we proposed in a previous study11) a functional model of a glial plasma membrane transporter. A reduction in ambient GABA concentration is assumed for a schizophrenia network. To adjust a level of ambient GABA, we systematically change the value of GABA transfer coefficient in the glial plasma membrane transporter model. At various ambient GABA levels, we record neuronal responses (spikes and membrane potentials) to a feature stimulus.

2 Neural Network Model

As shown in Figure 1a, cell assemblies consist of principal cells (P), GABAergic interneurons (Ia, Ib) and glial cells (glia). Each cell assembly (0 ≤ n ≤ 7) comprises twenty-cell units (P, Ia, Ib, glia). Each P cell receives excitatory inputs from other P cells and inhibitory inputs from Ib cells that receive excitatory inputs from P cells belonging to other cell assemblies. Each Ia cell receives an excitatory input from its accompanying P cell and synaptically connects to a glial cell. P cells synaptically connect to glial cells belonging to other cell assemblies. P cells receive an excitatory current as a graded sensory input (see τp in
The neural network model. (a) Neuronal circuitry. Fig. 1: conceptual scheme of GABA transport by glial plasma membrane. When stimulated, as shown in Figure 1b. (b) Graded sensory input. When presented with feature \( f_{inp} \), P cell assembly \( n \) receives the most intense input currents, its neighbors \( (n-1, n+1) \) the second most and so on, which is schematically indicated by the size of arrows. (c) A conceptual scheme of GABA transport by glial plasma membrane transporters. P and Ia cells synaptically connect to a glial cell. Transporters on the glial cell import (remove) GABA molecules from or export them into the extracellular space, depending on plasma membrane potential. The ambient GABA molecules are accepted by extrasynaptic GABA receptors and tonically inhibit a P cell.

Dynamic evolution of membrane potential of the \( i \)th P cell that belongs to cell assembly \( n \) is defined by

\[
eq -g_m^p u_i^p(n; t) - u_{rest}^p
\]

Dynamic evolution of membrane potential of the \( i \)th P cell that is an excitatory synaptic current from other P cells, \( I_{i}^{P,P}(n; t) \) an inhibitory synaptic current from Ib cells, \( I_{i,ext}^{P}(n; t) \) an inhibitory nonsynaptic current mediated by ambient GABA via extrasynaptic receptors, and \( I_{imp}^{P}(n; t) \) an excitatory input current that is provided when presented with sensory feature \( f_{inp} \). inp \( \in \{0, 1, 2, 3, ..., n, ..., M\} \). These currents are defined by

\[
I_{i}^{P,P}(n; t) = g_{AMP,A}^p(u_i^p(n; t) - u_{rev}^{AMP})
\]

\[
\times \sum_{j=1}^{N} w_{ij}^{P,P} I_{j}^{P}(n; t),
\]

\[
I_{i}^{P,Ib}(n; t) = -g_{GABA}^p(u_i^p(n; t) - u_{rev}^{GABA})
\]

\[
\times \sum_{j=1}^{N} w_{ij}^{P,Ib} I_{j}^{Ib}(n; t),
\]

\[
I_{i,ext}^{P}(n; t) = -g_{GABA}^p(u_i^p(n; t) - u_{rev}^{GABA})
\]

\[
\times \delta_{i,t,ext}(n; t),
\]

\[
I_{imp}^{P}(n; t) = \alpha_{P} e^{-\frac{(n-inp)^2}{\sigma^2}}.
\]

Dynamic evolution of membrane potential of the \( i \)th Ia and Ib cells that belong to cell assembly \( n \) is defined by

\[
eq -g_{m}^i I_{a,Ia}^i(n; t) - u_{rest}^a
\]

\[
\times I_{i,a,P}(n; t),
\]

\[
eq -g_{m}^i I_{b,Ib}^i(n; t) - u_{rest}^b
\]

\[
\times I_{i,b,P}(n; t),
\]

where \( I_{i,a,P}(n; t) \) and \( I_{i,b,P}(n; t) \) are excitatory synaptic currents from P cells. These currents are defined by

\[
I_{i,a,P}(n; t) = g_{AMP,A}^a(u_i^a(n; t) - u_{rev}^{AMP})
\]

\[
\times w_{i}^{a,P} r_{i}(n; t),
\]

\[
I_{i,b,P}(n; t) = g_{AMP,A}^b(u_i^b(n; t) - u_{rev}^{AMP})
\]

\[
\times \sum_{n'=0}^{M} w_{i}^{b,P}(n, n') r_{i}(n'; t),
\]

Dynamic evolution of membrane potential of the \( i \)th glial cell that belongs to cell assembly \( n \) is defined by

\[
eq -g_{m}^i I_{a,Ia}^i(n; t) - u_{rest}^I
\]

\[
\times I_{i,a,P}(n; t),
\]

\[
\times I_{i,b,P}(n; t),
\]

\[
eq -g_{GABA}^I(u_i^I(n; t) - u_{rev}^GABA) + I_{i}^{GL,Ia}(n; t).\]
Table 1: List of Parameters

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane capacitance of type K (K = P, Ia, Ib, glia) cell</td>
<td>K</td>
</tr>
<tr>
<td>Membrane conductance</td>
<td>g_m</td>
</tr>
<tr>
<td>Resting potential</td>
<td>w_Ia;P</td>
</tr>
<tr>
<td>Maximal conductance for type Z (Z = AMPA, GABA) receptor</td>
<td>g_z</td>
</tr>
<tr>
<td>Reversal potential</td>
<td>z</td>
</tr>
<tr>
<td>Number of cell-units within cell assemblies</td>
<td>N</td>
</tr>
<tr>
<td>Number of cell assemblies</td>
<td>M</td>
</tr>
<tr>
<td>Synaptic weight (strength) from j to i th P cell</td>
<td>w_{P}^{i,j}</td>
</tr>
<tr>
<td>Synaptic weight from j th Ib to i th P cell</td>
<td>w_{P}^{Ib;P}</td>
</tr>
<tr>
<td>Synaptic weight from i th P to Ia cell</td>
<td>w_{Ia;P}^{i,j}</td>
</tr>
<tr>
<td>Synaptic weight from i th P to Ib cell between different cell assemblies</td>
<td>w_{Ib;P}(n, n')</td>
</tr>
<tr>
<td>Synaptic weight from i th P to glial cell</td>
<td>w_{Gl;P}^{i,j}</td>
</tr>
<tr>
<td>Synaptic weight from i th Ia to glial cell</td>
<td>w_{Gl;Ia}^{i,j}</td>
</tr>
<tr>
<td>Amount of extrasynaptic GABAa receptors on P cell</td>
<td>δ_P</td>
</tr>
<tr>
<td>Input current</td>
<td>α_P</td>
</tr>
<tr>
<td>Broadness of input</td>
<td>τ_P</td>
</tr>
<tr>
<td>Channel opening rate for type Z (Z = AMPA, GABA) receptor</td>
<td>α_Z</td>
</tr>
<tr>
<td>Channel closing rate</td>
<td>β_Z</td>
</tr>
<tr>
<td>Steepness of sigmoid function for type Y (Y = P, Ia, Ib) cell</td>
<td>η_Y</td>
</tr>
<tr>
<td>Threshold of sigmoid function</td>
<td>ζ_Y</td>
</tr>
<tr>
<td>Decay constant for ambient GABA concentration</td>
<td>γ_{trn}</td>
</tr>
<tr>
<td>Basal ambient GABA concentration</td>
<td>[GABA]^0_{i,ext}</td>
</tr>
<tr>
<td>Maximal ambient GABA concentration</td>
<td>[GABA]_{max}</td>
</tr>
<tr>
<td>Minimal ambient GABA concentration</td>
<td>[GABA]_{min}</td>
</tr>
<tr>
<td>GABA transfer coefficient</td>
<td>T_{Gl}</td>
</tr>
<tr>
<td>Reversal potential of transporter</td>
<td>G_{Gl}^{i,ext}</td>
</tr>
</tbody>
</table>

where I_{i}^{Gl,P}(n; t) and I_{i}^{Gl,Ia}(n; t) are excitatory and inhibitory synaptic currents from P and Ia cells, respectively. These currents are defined by

\[
I_{i}^{Gl,P}(n; t) = -g_{AMPA}(u_{i}^{Gl}(n; t) - u_{AMPA}^{ext}) \times \sum_{n' = 0}^{M} w_{i}^{Gl,P}(n, n') r_{P}^{i}(n'; t), \quad (11)
\]

\[
I_{i}^{Gl,Ia}(n; t) = -g_{GABA}(u_{i}^{Gl}(n; t) - u_{GABA}^{ext}) \times w_{i}^{Gl,Ia} r_{Ia}^{i}(n; t). \quad (12)
\]

In these equations, r_{P}^{i}(n; t) is the fraction of AMPA receptors in the open state triggered by presynaptic action potentials of the jth P cell. r_{P}^{i}(n; t) and r_{Ia}^{i}(n; t) are the fractions of intrasynaptic GABAa receptors in the open state triggered by presynaptic action potentials of the jth Ib cell and Ia cell, respectively. r_{i,ext}^{P}(n; t) is the fraction of extrasynaptic GABAa receptors, located on the ith P cell, in the open state provoked by ambient GABA.

Receptor dynamics is described as

\[
dr_{P}^{i}(n; t) \frac{dt}{dt} = \alpha_{AMP}\left[Glut\right]_{j}(n; t)(1 - r_{P}^{i}(n; t)) - \beta_{AMP}r_{P}^{i}(n; t), \quad (13)
\]

\[
dr_{X}^{i}(n; t) \frac{dt}{dt} = \alpha_{GABA}\left[GABA\right]_{j}^{X}(n; t)(1 - r_{X}^{i}(n; t)) - \beta_{GABA}r_{X}^{i}(n; t), \quad (14)
\]

\[
dr_{i,ext}^{P}(n; t) \frac{dt}{dt} = \alpha_{GABA}\left[GABA\right]_{i,ext}^{P}(n; t) \times \left(1 - r_{i,ext}^{P}(n; t)\right) - \beta_{GABA}r_{i,ext}^{P}(n; t), \quad (15)
\]

where \[Glut\]_{j}(n; t) and \[GABA\]_{j}^{X}(n; t) are concentrations of glutamate and GABA in synaptic cleft, respectively. \[Glut\]_{j}(n; t) = 1mM and \[GABA\]_{j}^{X}(n; t) = 1mM for 1 ms when the presynaptic jth P cell and type X cell fire, respectively. Otherwise, \[Glut\]_{j}(n; t) = 0 and \[GABA\]_{j}^{X}(n; t) = 0.

Probability of neuronal firing is defined by

\[
Prob[Y_{j}(n; t); firing] = \frac{1}{1 + e^{-\eta_{Y}(u_{j}(n; t) - \zeta_{Y})}}. \quad (Y = P, Ia, Ib) \quad (16)
\]

When a cell fires, its membrane potential is depolarized to -10 mV, which is kept for 1 msec and then reset to the resting potential.

Concentration of ambient GABA around the ith P cell that belongs to cell assembly n is defined by

\[
d[GABA]^{P}_{i,ext}(n; t) \frac{dt}{dt} = -\gamma_{trn}([GABA]^{P}_{i,ext}(n; t) - [GABA]^{0}_{i,ext}) + T_{Gl}([GABA]_{max} - [GABA]^{P}_{i,ext}(n; t)) \times \left\{ [GABA]^{P}_{i,ext}(n; t) - [GABA]^{min}\right\} \times (u_{i}^{Gl}(n; t) - u_{Gl}^{ext}). \quad (17)
\]

For these parameters, see our previous studies\cite{12, 13, 14, 15, 16} and Table 1.

3 Result

We show how GABAergic gliotransmission affects neuronal behavior, and examine whether and how a reduction in ambient GABA concentration due to a deficit in GABAergic gliotransmission deteriorates perceptual performance of the schizophrenia network. Figure 2a shows membrane potentials of (see the top traces) and ambient GABA concentrations around (see the bottom traces) P cells belonging to respective cell assemblies (0 ≤ n ≤ 7) when presented with sensory feature f3. Due to the graded sensory input (τ_P
stimulus-irrelevant P cells tend to respond at the onset of the stimulus (e.g., see n = 2, 4). Nonetheless, the network can finally tune to the input (see n = 3).

As shown in Figure 2a (bottom), the cessation of firing in the stimulus-irrelevant P cells arises largely from the enhanced ambient GABA-mediated tonic inhibition (see the traces marked by "n = 3"). Interestingly, the ambient GABA concentration around the stimulus-relevant P cells is reduced (see the trace marked by "n = 3"), ensuring their responsiveness to the stimulus. Figure 2b shows membrane potentials (top) and ambient GABA concentrations (bottom) in the schizophrenia network. The value of GABA transfer coefficient (see $T_{Gl}$ in equation 17 and Table 1) was decreased from $15 \times 10^8$ to $1 \times 10^8$, which may correspond to transporter-deficient glial cells. This causes a deficit in GABAergic gliotransmission, impairing ambient GABA augmentation (see the bottom traces). Due to the insufficient increase in ambient GABA levels, the stimulus-irrelevant P cells continue firing throughout the stimulation period (see the traces for n = 2, 4 at the top). Figure 2c shows stimulus-evoked neuronal (population-averaged P cell firing) activities recorded in respective cell assemblies ($0 \leq n \leq 7$) of the control network (open bars) or the schizophrenia network (filled bars). These results indicate that the tuning performance of the schizophrenia network is deteriorated compared to the control network.

We show how the impairment in augmenting ambient GABA concentration due to a deficit in GABAergic gliotransmission causes a broadening of sensory tuning in the schizophrenia network. Figure 3a shows the dependence of stimulus-evoked neuronal (population-averaged P cell firing) activity (top) and ambient GABA concentration (bottom) on GABA transfer coefficient ($T_{Gl}$; see equation 17 and Table 1), recorded in each cell assembly ($0 \leq n \leq 7$). These results indicate that the larger transfer coefficient value could strongly suppress stimulus-irrelevant P cell activities, for which the augmentation of ambient GABA is responsible (bottom; see n ≠ 3). As shown in Figure 3b, if the P-to-glia circuit is cut off, the neuronal responses show no significant change (top), which is due largely to the less modulation of ambient GABA levels (bottom). If the Ia-to-glia circuit is cut off, the lower level of ambient GABA around the stimulus-relevant P cells cannot be ensured (see the open circle for n=3 at the bottom of Figure 3c) and thus their responses to the stimulus are depressed (see the open circle for n=3 at the top of Figure 3c). These results indicate that the GABAergic gliotransmission mechanism well works for sensory tuning.

4 Discussion

We showed that the GABAergic gliotransmission mechanism could regulate local ambient GABA levels. Namely, it augmented ambient GABA around stimulus-irrelevant principal cells while reducing ambient GABA around stimulus-relevant principal cells (see Figure 3a: bottom), thereby ensuring their selective responsiveness to the applied feature stimulus. The GABAergic gliotransmission mechanism,
Fig. 3: Influence of GABA transporter on tuning performance of the network. (a) Top: Dependence of stimulus-evoked neuronal (population-averaged P cell firing) activity on GABA transfer coefficient\( (T_{\text{Gl}}; \text{see equation 17 and Table 1}) \), recorded in each cell assembly \((0 \leq n \leq 7)\). Bottom: Dependence of ambient GABA concentration on \(T_{\text{Gl}}\). (b) Dependence of stimulus-evoked neuronal activity and ambient GABA concentration on \(T_{\text{Gl}}\) in which the P-to-glia circuit was cut off (see Figure 1). (c) Dependence of stimulus-evoked neuronal activity and ambient GABA concentration on \(T_{\text{Gl}}\) in which the Ia-to-glia circuit was cut off.

proposed here, may have an important role in the regulation of local ambient GABA levels.

The P-glia coupling had a role in increasing a level of ambient GABA around stimulus-irrelevant P cells. The Ia-glia coupling had a role in decreasing a level of ambient GABA around stimulus-relevant P cells. These couplings achieved combinatorial regulation of local ambient GABA levels, by which we could show how the poor control of ambient GABA concentration due to deficient GABAergic gliotransmission leads to the deteriorated sensory tuning performance in schizophrenic patients\(^1, 2, 3\). To the best of our knowledge, these specific couplings between different (P, Ia) cells and glia have not been observed. They were assumed based on studies\(^17, 18, 19\) that indicated a variety of glutamatergic and GABAergic neuron-glia projections.

As is well known, GABA\(\alpha\) receptors mediate both phasic and tonic inhibition in the cortex. It has been suggested that in addition to the alteration of intrasynaptic GABA-mediated phasic inhibition, the alteration of extrasynaptic (ambient) GABA-mediated tonic inhibition has significant relevance to schizophrenia\(^20\). A decrease in tonic inhibition is expected when the expression of extrasynaptic receptor subunits such as the \(\delta\) subunit decreases in the visual cortex with schizophrenia\(^21\). In the present study, we showed that a reduction in tonic GABA strength due to deficient gliotransmission resulted in poor tuning ability to a sensory stimulus (see Figure 3). We suggest that in addition to the phasic GABA mechanism the gliotransmission-mediated, tonic GABA mechanism, proposed here, may be another critical component in etiology of schizophrenia.

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