Comparable GABAergic Mechanisms of Hippocampal Seizurelike Activity in Posttetanic and Low-Mg\(^{2+}\) Conditions

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Fujiiwara-Tsukamoto, Yoko, Yoshihiko Isomura, and Masahiko Takada. Comparable GABAergic mechanisms of hippocampal seizurelike activity in posttetanic and low-Mg\(^{2+}\) conditions. J Neurophysiol 95: 2013–2019, 2006. First published December 7, 2005; doi:10.1152/jn.00238.2005. It is known that GABA is a major inhibitory neurotransmitter in mature mammalian brains, but the effect of this substance is sometimes converted into depolarizing or even excitatory when the postsynaptic Cl\(^-\) concentration becomes high. Recently we have shown that seizurelike afterdischarge induced by tetanic stimulation in normal extracellular fluid (posttetanic afterdischarge) is mediated through GABAergic excitation in mature hippocampal CA1 pyramidal cells. In this study, we examined the possible contribution of similar depolarizing/excitatory GABAergic input to the CA1 pyramidal cells to the seizurelike afterdischarge induced in a low extracellular Mg\(^{2+}\) condition, another experimental model of epileptic seizure activity (low-Mg\(^{2+}\) afterdischarge). Perfusion of the GABA\(_A\) antagonist bicuculline abolished the low-Mg\(^{2+}\) afterdischarge, but not the interictal-like activity, in most cases. Each oscillatory response during the low-Mg\(^{2+}\) afterdischarge was dependent on Cl\(^-\) conductance and contained an F\(^-\)-insensitive depolarizing component in the pyramidal cells, thus indicating that the afterdischarge response may be mediated through both GABAergic and non-GABAergic transmissions. In addition, local GABA application to the recorded cells revealed that GABA responses were indeed depolarizing during the low-Mg\(^{2+}\) afterdischarge. Furthermore, the GABAergic interneurons located in the strata pyramidale and oriens fired in oscillatory cycles more actively than those in other layers of the CA1 region. These results suggest that the depolarizing GABAergic input may facilitate oscillatory synchronization among the hippocampal CA1 pyramidal cells during the low-Mg\(^{2+}\) afterdischarge in a manner similar to the expression of the posttetanic afterdischarge.

INTRODUCTION

It has been revealed that GABA may act as a depolarizing/excitatory neurotransmitter in specific physiological and pathological circumstances, such as early development (Ben-Ari et al. 1989) and epilepsy (Cohen et al. 2002). For example, repetitive electrical stimulation (tetanization) induces large GABA\(_A\)-dependent depolarization (Alger and Nicoll 1979), probably because of the collapsed Cl\(^-\) gradient and preserved HCO\(_3^-\) gradient (Staley and Proctor 1999; Staley et al. 1995) and extracellular K\(^+\) accumulation (Kaila et al. 1997; Smirnov et al. 1999), in subcellular compartments of mature hippocampal pyramidal cells (Vreugdenhil et al. 2005). Using a Cl\(^-\) imaging technique, we have in fact shown that tetanic stimulation results in a transient increase in the intracellular Cl\(^-\) concentration in the hippocampal pyramidal cells (Isomura et al. 2003b), which may make the reversal potential of GABA\(_A\) responses much higher than the resting membrane potential. Moreover, intense tetanization induces long-lasting, seizure-like rhythmic synchronization (posttetanic afterdischarge) after the large depolarization in the pyramidal cells (Bragin et al. 1997; Isomura et al. 2003a; Rafiq et al. 1993; Stasheff et al. 1989, 1993a,b), which is also mediated through GABA\(_A\) activation (Higashima et al. 1996, 2000; Perez Velazquez and Carlen 1999). We have recently reported that oscillatory depolarizing responses in the pyramidal cells during the afterdischarge may be evoked by direct GABAergic input (Fujiwara-Tsukamoto et al. 2003; Kaneda et al. 2005). In another work (Fujiwara-Tsukamoto et al. 2004), we have further shown that a group of interneurons that are located in the stratum oriens and stratum pyramidale dominantly contribute to the expression of such GABA-dependent seizurelike afterdischarge. Thus the excitatory GABAergic transmission seems to play a critical role in the posttetanic model of epileptic seizure activity.

On the other hand, it is well known that in a low extracellular Mg\(^{2+}\) condition, ictal- (seizure-) and interictal-like activities are evoked spontaneously or by one or two electrical stimuli in the hippocampal pyramidal cells in vitro (ictal-like, Anderson et al. 1986; DeLorenzo et al. 1998; Traub et al. 1994: interictal-like, Mody et al. 1987; Tancredi et al. 1990). Although enhancement of N-methyl-D-aspartate (NMDA) receptor conductance is essential for the low Mg\(^{2+}\)-induced generation of these epileptic activities, the functional contribution of GABA\(_A\) receptors to their generation still remains controversial. It has been reported that incubation of the pyramidal cells in low-Mg\(^{2+}\) medium results in reduced GABA\(_A\) conductance (Whittington et al. 1995) and that application of GABA or GABA\(_A\) agonists abolishes the seizurelike activity (Pfeiffer et al. 1996). In contrast, recent pharmacological studies using GABA\(_A\) antagonists or carbonic anhydrase inhibitors have pointed out that GABA might play a rather active role in such epileptic phenomena as a potential excitatory transmitter (Köhling et al. 2000; Perez Velazquez 2003; Quilichini et al. 2002). Nevertheless, these observations have not as yet excluded the possibility that GABA may not be required for driving each oscillatory cycle of the seizurelike activity, but just for initial triggering of the seizurelike activity in a low-Mg\(^{2+}\) condition.

In this study, we examined 1) whether oscillatory depolarizing responses in the hippocampal pyramidal cells might...
indeed be mediated directly through depolarizing/excitatory GABAergic input during the low Mg$^{2+}$-induced seizure-like activity (low-Mg$^{2+}$ afterdischarge) and 2) what the difference or similarity is between GABAergic mechanisms of the posttetanic and low-Mg$^{2+}$ afterdischarges, by comparing these two models in the same experimental environment as used previously (Fujiwara-Tsukamoto et al. 2003, 2004).

METHODS

Hippocampal slices (400 μm thick) were prepared from ether-anesthetized Wistar rats (P20–P27) with a microslicer (DTK-1500, Dosaka EM, Kyoto, Japan), and the CA1 region was routinely isolated from the CA3 and subiculum regions (CA1-isolated slices; Fujiwara-Tsukamoto et al. 2003, 2004; Fig. 1A). For the induction of posttetanic afterdischarges, each slice was allowed to recover for >1 h in normal artificial cerebrospinal fluid (ACSF), consisting of 124 NaCl, 2.5 KCl, 200 mM NaHCO$_3$, 1.2 MgSO$_4$, 25 D-glucose (in mM) and was saturated with 95% O$_2$-5% CO$_2$ gas (Isomura et al. 2003a). For the induction of low-Mg$^{2+}$ afterdischarges, on the other hand, each slice was incubated for >3 h in Mg$^{2+}$-free ACSF in which MgSO$_4$ was omitted from the normal ACSF. The incubated slices were transferred to a submerged-type recording chamber circulated continuously with the normal or Mg$^{2+}$-free ACSF in which MgSO$_4$ was omitted from the normal ACSF. The incubated slices were transferred to a submerged-type recording chamber circulated continuously with the normal or Mg$^{2+}$-free ACSF at 30–32°C. Tetanic stimulation (tetanus; 100 Hz for 0.5 s, intensity 400 μA, duration 400 μs) or paired-pulse stimulation (10 Hz for 0.1 s) was delivered at 7- to 10-min intervals to induce the posttetanic or low-Mg$^{2+}$ afterdischarge, respectively, by a monopolar glass stimulating electrode (0.5–1 MΩ, filled with 2.5 M NaCl) placed in the stratum pyramidale. Recorded potentials [resting membrane potential (in mV, values not corrected for liquid junction potential); pyramidal cells, −59.6 ± 3.3 mV in normal ACSF, −59.9 ± 2.3 in Mg$^{2+}$-free ACSF; interneurons, −58.4 ± 5.6 (s. radium/lacunosum-molecular), −56.4 ± 5.3 (s. oriens/pyramidal) in Mg$^{2+}$-free ACSF] were recorded in the current-clamp mode (I = 0) with a patch-clamp amplifier (Axopatch 1D or Axopatch 200B, Axon Instruments, Union City, CA), through glass patch electrodes filled with a low-CI$^-$ internal solution containing (in mM) 140 K-glucuronate, 2 NaCl, 1 MgCl$_2$, 10 HEPES, 0.2 EGTA, 2 5'-ATP Na$_2$, 0.5 GTP Na$_2$, and 10 biocytin (pH 7.4, 5–10 MΩ). Gramicidin (20–100 μg/ml; Sigma, St. Louis, MO) was added to the low-CI$^-$ internal solution for perforated patch-clamp recordings (Lamsa and Taira 2003; Yamada et al. 2004). In re-patch-clamp experiments using a high CI$^-$ internal solution, KCl was substituted for K-glucuronate. An internal solution used for intracellular blockade of GABA$_A$ receptors consisted of (in mM) 140 KF, 10 HEPES, 0.2 EGTA, and 10 biocytin. Voltage-clamp recordings were also performed using another low CI$^-$ internal solution containing (in mM) 132 Cs-glucuronate, 2 NaCl, 1 MgCl$_2$, 10 HEPES, 2 EGTA, 2 5'-ATP Na$_2$, 0.5 GTP Na$_2$, 10 biocytin, and 5 MQ-314 (Alomone Labs, Jerusalem, Israel) (Fujiwara-Tsukamoto et al. 2003). For simultaneous whole cell and extracellular recordings, field potentials were additionally recorded with one of the amplifiers through glass electrodes (2–5 MΩ, filled with 2.5 M NaCl) placed in the s. pyramidale. Recorded signals were low-pass-filtered at 3–5 kHz and digitized at 5 kHz with an A/D interface (Digidata 1200, Axon Instruments). In some experiments, biocytin-loaded neurons were visualized by an avidin-biotin-horseradish peroxidase complex (ABC) method to confirm their somatic location and dendritic/axonal distributions (Fujiwara-Tsukamoto et al. 2004).

Bicuculline and GABA were purchased from Sigma; n-2-amino-5-phosphonopentanoic acid (DL-AP-5) and CGP55845 were from Tocris Cookson (Ballwin, MO); and other reagents were from Nacalai Tesque (Kyoto, Japan). GABA (0.1 mM in saline) was applied to the soma of recorded pyramidal cells briefly and repeatedly by pressure (5–10 psi, 10–150 ms; Picospritzer II, General Valve).

FIG. 1. Sensitivity of posttetanic and low Mg$^{2+}$-induced seizure-like afterdischarges to N-methyl-d-aspartate (NMDA) and GABA$_A$ receptor antagonists. A: schematic diagram of extracellular [field potential (FP)] and whole cell [membrane potential (MP)] recordings in hippocampal CA1-isolated slices. Rec., recording electrode; Stim., stimulating electrode; DG, dentate gyrus; S, subiculum. B: FP recordings of posttetanic (left) and low-Mg$^{2+}$ (right) afterdischarges before (top), during (middle), and after (bottom) bath application of the NMDA receptor antagonist DL-AP-5 (50 μM). Afterdischarge was induced by tetanic stimulation in normal artificial cerebrospinal fluid (ACSF; posttetanic; 50 pulses at 100 Hz; thick bars) or by paired-pulse stimulation in Mg$^{2+}$-free ACSF (low Mg$^{2+}$; 2 pulses at 10 Hz; filled circles). Scale bars: 2 s, 0.2 mV. C: FP and MP recordings of posttetanic (left) and low-Mg$^{2+}$ (right) afterdischarges before (top), during (middle), and after (bottom) bath application of the GABA$_A$ receptor antagonist bicuculline (25 μM). Membrane potentials were recorded from pyramidal cells; their action potentials are truncated. *Interictal-like activity. Scale bars: 2 s, 0.5 mV for FP and 8 mV for MP. Each inset shows 1 cycle of the oscillatory responses of afterdischarge in the left trace. Scale bars: 50 ms, 10 mV.
Field potential and membrane potential recordings showed that, in the hippocampal CA1-isolated slice preparations, seizure-like synchronous oscillations lasting 10–40 s were readily induced not only by tetanic stimulation in normal ACSF (posttetanic afterdischarge) but also by paired-pulse stimulation in Mg\(^{2+}\)-free ACSF (low-Mg\(^{2+}\) afterdischarge; Fig. 1), indicating that both types of the afterdischarges are inducible in the local CA1 neuronal circuit. Bath application of the NMDA receptor antagonist DL-AP-5 abolished the low-Mg\(^{2+}\) afterdischarge reversibly (n = 3), whereas it had only a small effect on the posttetanic afterdischarge (n = 6; Fig. 1B; see also Fujiwara-Tsukamoto et al. 2003; Traub et al. 1994). On the other hand, application of the GABA\(_A\) receptor antagonist bicuculline blocked the posttetanic afterdischarge completely in all of the nine slices examined and the low-Mg\(^{2+}\) afterdischarge in five of seven slices (Fig. 1C). The remaining two slices in the low-Mg\(^{2+}\) condition exhibited rather enhanced afterdischarge activity. Similar results were obtained with another GABA\(_A\) receptor antagonist 50 \(\mu\)M picrotoxin (n = 3; 1 blocked and 2 enhanced). Such an enhanced afterdischarge might be caused by another (probably disinhibition-induced) type of seizure-like activity (Borck and Jefferys 1999). In addition, bicuculline-insensitive, spontaneous interictal-like bursting activity was frequently observed in all of the slices in the low-Mg\(^{2+}\) condition (Fig. 1C), which may be dependent on NMDA receptor activation (Mody et al. 1987; Tancrède et al. 1990). Moreover, application of the positive allosteric GABA\(_A\) modulator, 50 \(\mu\)M pentobarbital sodium enormously elongated an initial giant GABA-dependent depolarization \(\leq 30\) s, which normally lasted only several seconds, and further enlarged each oscillatory response of the subsequent seizure-like activity in both the posttetanic and the low-Mg\(^{2+}\) conditions (posttetanic, n = 4; low Mg\(^{2+}\), n = 4; data not shown). These results have confirmed that GABA transmission certainly contributes not only to the generation of posttetanic afterdischarges, but also to the generation of low-Mg\(^{2+}\) afterdischarges within a local network of the CA1 region, which is consistent with previous data in whole hippocampal slice preparations (Köhling et al. 2000).

Next, we examined whether the pyramidal cells might receive direct GABAergic input during the low-Mg\(^{2+}\) afterdischarge, as shown in the case of the posttetanic afterdischarge (Fujiwara-Tsukamoto et al. 2003, 2004). Our re–patch-clamp technique to change internal ionic environments (Fujiwara-Tsukamoto et al. 2003) clearly revealed that the oscillatory responses recorded in the pyramidal cells were remarkably enhanced by a large increase in the intracellular Cl\(^-\) concentration during both the posttetanic and the low-Mg\(^{2+}\) afterdischarges [Fig. 2A: mean spiking activity (spikes/cycle); posttetanic, control 0.14 ± 0.37, high Cl\(^-\) 1.29 ± 0.92 (n = 6), P < 0.03; low Mg\(^{2+}\), control 0.99 ± 0.75, high Cl\(^-\) 1.75 ± 0.20 (n = 6), P < 0.05]. This suggests that the pyramidal cells are likely to receive Cl\(^-\)-conductance-dependent synaptic input, probably mediated through GABA\(_A\) receptors, in each cycle of the afterdischarges. Repeated local application of GABA to the pyramidal cells recorded with low-Cl\(^-\) electrodes showed that external hyperpolarizing responses were temporarily converted into depolarizing for 10–50 s after the induction of posttetanic and low-Mg\(^{2+}\) afterdischarges [conversion time (s); posttetanic 30 ± 7 (n = 12); low Mg\(^{2+}\) 39 ± 18 (n = 10)]. Such transiently depolarizing GABA responses were observed more obviously in a gramicidin-perforated patch-clamp recordings, which would not affect intracellular Cl\(^-\) environment (Fig. 2B: posttetanic, n = 6; low Mg\(^{2+}\), n = 6). The depolarizing GABA responses in the perforated patch-clamp mode usually lasted 25 s to several minutes in both conditions. In particular, they were sometimes already depolarizing even at a resting period in the low-Mg\(^{2+}\) condition (n = 3 of 6; Fig. 2B, inset). However, unlike the posttetanic condition (Fujiwara-Tsukamoto et al. 2003), intracellular blockade of GABAergic transmission by F\(^-\) ions, a nonspecific GABA\(_A\) blocker, failed to abolish the oscillatory depolarizing responses completely in the low-Mg\(^{2+}\) condition [Fig. 2C: mean amplitude of residual oscillatory responses in F\(^-\)-treated pyramidal cells (mV); posttetanic 0.1 ± 0.5 (n = 7); low Mg\(^{2+}\) 4.1 ± 2.4 (n = 6); P < 0.01]. Furthermore, voltage-clamp recordings revealed that the reversal potential of exogenous GABA responses (Fig. 2D; n = 6, –65.9 ± 4.8 mV) was largely shifted toward the spike threshold during the low-Mg\(^{2+}\) afterdischarge (–44.4 ± 7.5 mV, P < 0.001) and that the reversal potential of the afterdischarge was still higher than that of the GABA responses (–14.4 ± 4.2 mV, P < 0.001). These results imply that the oscillatory depolarization of low-Mg\(^{2+}\) afterdischarges may consist of not only a GABAergic but also a non-GABAergic, putatively glutamatergic, component. In other words, GABA is likely to participate, at least partly, in the oscillatory depolarizing responses of the low-Mg\(^{2+}\) as well as the posttetanic afterdischarge.

Given that such GABAergic input to the pyramidal cells actively drives both the posttetanic and the low-Mg\(^{2+}\) afterdischarges, GABAergic interneurons should discharge synchronously with the pyramidal cells during these afterdischarges. In fact, we have recently shown that the interneurons located in the s. oriens or pyramidale (SO/SP interneurons), regardless of their subtypes, fire much more actively than those in the s. radiatum or lacunosum-moleculare (SR/SLM interneurons) during the posttetanic afterdischarge (Fujiwara-Tsukamoto et al. 2004). Therefore we examined whether there might be any difference in the firing activity between these two interneuron groups during the afterdischarge induced in the low-Mg\(^{2+}\) condition. Figure 3A shows different membrane potential responses in two representative non–fast-spiking (non-FS) interneurons during the low-Mg\(^{2+}\) afterdischarge; a non-FS interneuron located in the SLM exhibited no afterdischarge-associated responses, whereas a non-FS interneuron in the SO displayed robust bursting activities, synchronous with population spikes, during the low-Mg\(^{2+}\) afterdischarge. In the whole time-course of the low-Mg\(^{2+}\) afterdischarge, the spiking activity in SO/SP interneurons (n = 13, including 8 non-FS interneurons) was significantly larger than that in SR/SLM interneurons (n = 20, including 19 non-FS interneuron) [Fig. 3B, left and middle: mean spike number (spikes/cycle); SR/SLM 1.57 ± 1.82 vs. SO/SP 5.62 ± 4.06, P < 0.005; mean
spiking probability (% in cycle); SR/SLM 52.7 ± 40.6 vs. SO/SP 90.2 ± 20.4, P < 0.002]. These non-FS subgroups also showed similar differences between SR/SLM and SO/SP interneurons (spike number, P < 0.05; probability, P < 0.001). Furthermore, spikes in the SO/SP interneurons, but not in the SR/SLM interneurons, were highly time-locked to the field population spikes associated with synchronous discharges in the pyramidal cells (Fig. 3B, right), although there were spontaneous spikes observed at the interval of oscillatory activities in both of the interneuron groups. The spiking in 5 of the 13 SO/SP interneurons (including 2 FS cells) clearly preceded the onset of field afterdischarge responses, suggesting that they may drive the pyramidal cells in each cycle of the afterdischarges. Such synchronized interneuron activities depending
on their somatic locations during the low-Mg\textsuperscript{2+} afterdischarge were very comparable with those during the posttetanic afterdischarge (see Fujiwara-Tsukamoto et al. 2004), and, therefore, a similar or common GABAergic mechanism may underlie the local generation of these seizure-like synchronous oscillations.

**DISCUSSION**

In this study, we defined the similarity of the posttetanic and low-Mg\textsuperscript{2+} conditions in the contribution of GABAergic transmission to seizure-like afterdischarges. For the induction of both types of the afterdischarges, hippocampal pyramidal cells are most likely to receive substantial GABAergic input that is depolarizing or probably excitatory in each oscillatory cycle of afterdischarges. Moreover, during these afterdischarges, SO/SP interneurons exhibit synchronous firing with the pyramidal cells in each oscillatory cycle (see also Fujiwara-Tsukamoto et al. 2004). Our results strongly support the notion that GABA may actively participate in the generation of both the posttetanic and the low-Mg\textsuperscript{2+} afterdischarges in a similar manner. However, there are several minor differences between these afterdischarges: (1) in some cases, seizure-like activity was still inducible under the blockade of GABA\textsubscript{A} receptors in the low-Mg\textsuperscript{2+} condition, indicating the existence of a different, GABA-independent epileptiform activity (Borck and Jefferys 1999), and (2) the pyramidal cells could directly receive putatively glutamatergic input, which might depend on enhanced NMDA receptor activation, during the low-Mg\textsuperscript{2+}, but not the posttetanic, afterdischarge. As we used the CA1-isolated slices here (see Fig. 1A), such direct glutamatergic input may be mediated through recurrent collaterals of the CA1 pyramidal cells (Crépel et al. 1997). Hence, principally non-GABAergic excitatory inputs to the pyramidal cells are likely to drive their oscillatory responses, in cooperation with synchronous GABAergic depolarizing/excitatory inputs to the same neurons, in the low-Mg\textsuperscript{2+} condition.

The posttetanic afterdischarge was readily induced even in naive slice preparations, i.e., by the first tetanus in normal ACSF, whereas the low-Mg\textsuperscript{2+} afterdischarge required prior slice incubation in Mg\textsuperscript{2+}-free ACSF for ≈3 h. In the posttetanic condition, intense GABA\textsubscript{A} stimulation during tetanization often triggers massive Cl\textsuperscript{-} influx into the pyramidal cells, allowing GABA\textsubscript{A} responses to turn temporarily into depolarizing (Isomura et al. 2003b; Staley and Proctor 1999; Staley et al. 1995). Such GABA\textsubscript{A}-triggered, instantaneous depolarization is capable of lasting several minutes in the pyramidal cells (Chabwine et al. 2004). On the other hand, the GABAergic depolarization in the low-Mg\textsuperscript{2+} condition may require not only GABA\textsubscript{A}-mediated Cl\textsuperscript{-} influx, but also a decrease in an ability of Cl\textsuperscript{-} extrusion caused by down-regulation of Cl\textsuperscript{-} transporters, spending several hours. In fact, Rivera et al. (2002, 2004) have recently shown that spontaneous interictal-like activity generated in the low-Mg\textsuperscript{2+} condition downregulates mRNA expression and protein synthesis of the K\textsuperscript{+}\textendash Cl\textsuperscript{-} cotransporter KCC2 that mediates extrusion of Cl\textsuperscript{-} ions, which depends on activation of the brain-derived neurotrophic factor–TrkB signaling pathway. Taken together, rapid Cl\textsuperscript{-} influx and/or impaired Cl\textsuperscript{-} extrusion seem to be essential for GABA\textsubscript{A}-dependent depolarization during the expression of low Mg\textsuperscript{2+}-induced seizure-like afterdischarges.

We have revealed that SO/SP interneurons are more deeply involved than SR/SLM interneurons in GABA-dependent neuronal synchronization during the posttetanic afterdischarge. Both the GABAergic SO/SP interneurons and the glutamatergic pyramidal cells are necessary to form a “positive feedback” circuit for synchronization of their firing activities (Fujiwara-Tsukamoto et al. 2004). Recently, Lamsa and Taira (2003) have reported that tetanic stimulation also induces long-lasting...
GABAergic excitation in SO/SP interneurons. In the low-Mg$^{2+}$ afterdischarge, SO/SP interneurons fire synchronously with the pyramidal cells, suggesting these interneurons may interact with the pyramidal cells and probably with other SO/SP interneurons to express the neuronal synchronization in the low-Mg$^{2+}$ condition. Thus it is likely that the depolarizing/excitatory GABAergic transmission by SO/SP interneurons may play a common role in the expression of such experimental seizure-like activities. Although a pharmacological abolishment of GABA functions also often results in experimental epileptogenesis (Borck and Jefferys 1999), GABAergic neurons and their terminals are actually well preserved in the hippocampus of human epilepsy patients (Babb et al. 1989), and, indeed, an epileptic activity is driven by the depolarizing GABAergic transmission in human limbic epileptogenic tissues (Cohen et al. 2002). Therefore such a drastic functional conversion of GABAergic transmissions might actually cause or augment synchronous excitation of glutamatergic neurons, leading to human temporal lobe epilepsy eventually.

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