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Original Article

Experimental Neurobiology

Disinhibitory Action of Astrocytic GABA at the Perforant Path to Dentate Gyrus Granule Neuron Synapse Reverses to Inhibitory in Alzheimer's Disease Model

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Like neurons, astrocytes produce and release GABA to influence neuronal signaling. At the perforant path to dentate gyrus granule neuron synapse, GABA from astrocyte was found to be a strong inhibitory factor, which impairs synaptic transmission, synaptic plasticity and memory in Alzheimer's disease. Although astrocytic GABA is observed in many brain regions, its physiological role has not been clearly demonstrated yet. Here, we show that astrocytic GABA exerts disinhibitory action to dentate granule neurons by targeting $GABA_B$ receptors of GABAergic interneurons in wild-type mice. This disinhibitory effect is specific to a low intensity of electrical stimulation at perforant path fibers. Inversely in Alzheimer's disease model mice, astrocytic GABA targets $GABA_A$ receptors and exerts inhibitory action by reducing release probability of glutamatergic perforant path terminals. These results suggest that astrocytic GABA differentially modulates the signaling from cortical input to dentate gyrus under physiological and pathological conditions.

Key words: Alzheimer's disease, Astrocyte, Dentate gyrus, GABA, Perforant path

INTRODUCTION

Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the mammalian brain, has two modes of release: phasic and tonic [1]. While phasic release is mediated by synaptic vesicles in GABAergic neurons, tonic release is channel-mediated, a sustained form of release and originated from glial cells [2-4]. Unlike neurons, which convert glutamate to GABA by glutamate decarboxylases (GADs), glial cells utilize putrescine to produce GABA [5]. Among the enzymes involved in putrescine degradation pathway, monoamine oxidase B (MAOB) is a key enzyme [6] that is responsible for glial GABA production in the cerebellum and striatum [7]. Treatment of MAOB inhibitor or gene silencing of *MAOB* effectively suppresses GABA production and release from glial cells [7, 8]. The content of glial GABA measured by immunohistochemistry varies in different regions of the brain and is known to positively correlate with a degree of tonic inhibition onto neurons [9]. However, physiological relevance of

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glial GABA in various brain regions and specific neural circuits remains unknown.

Recently, we have shown a novel function of glial GABA in a pathological condition using two mouse models of Alzheimer's disease [8]. In the molecular layer of dentate gyrus (DG), diseased astrocytes produce abundant amount of GABA which is further released and inhibits excitatory synaptic transmission at the perforant path (PP) to DG granule neuron synapse [8]. Because the DG is the gateway of cortical input to the hippocampus [10] and is essential for the formation and recall of memory [11], that GABA binds to neuronal $GABA_A$ and $GABA_B$ receptors and results in impaired learning and memory in Alzheimer's disease. Accordingly, suppressing astrocytic GABA production by oral administration of MAOB inhibitors rescues excitatory synaptic transmission and improves memory in Alzheimer's model [8]. However, what proportion of GABA from reactive astrocyte targets $GABA_A$ and $GABA_B$ has not been determined.

How about the role of astrocytic GABA under physiological condition? Although the content of astrocytic GABA is much lower under normal condition than that of diseased astrocytes, normal astrocytes show moderate levels of intracellular GABA [9] and granule neurons show a small but significant level of tonic inhibition current in wild type mouse [8]. Interestingly, in wild-type mice, suppressing astrocytic GABA production was shown to decrease the amplitude of evoked excitatory postsynaptic currents (eEPSCs) at low intensity of PP stimulation [8], suggesting an excitatory action of astrocytic GABA. Considering the presence of GABAergic interneurons in the molecular layer of DG [12], it is possible that the excitatory action of astrocytic GABA is by disinhibition. Another possibility is that it could be due to the $GABA_A$-mediated depolarizing effect if the intracellular chloride concentration is high [13, 14]. However, these possibilities have not been examined yet. Here, we investigated a physiological role of astrocytic GABA in the DG and compared its mechanism with a pathological condition by adopting APP/PS1 mice, a popular model of Alzheimer's disease.

MATERIALS AND METHODS

Animals

All animal care and handling was performed according to the directives of the Animal Care and Use Committee of KAIST (Daejeon, Korea) and the Institutional Animal Care and Use Committee of KIST (Seoul, Korea). APPswe/PSEN1dE9 (APP/PS1; stock number 004462, Jackson Laboratory, USA) mice were maintained as hemizygotes by repeated backcrossing with B6C3 F1 mice. Both sexes of 8- to 13-month-old transgenic mice and wild-type littermates were used for study. All experiments were performed with gender- and age-matched controls. For oral administration of selegiline, the mice were provided with water (control) or selegiline solution *ad libitum*, refreshed every two or three days. The selegiline solution was prepared by dissolving 10 mg of r-(–)-deprenyl hydrochloride (Sigma, USA) in 150 ml drinking water. In this condition, the dose was calculated as 5~10 $mg\,kg^{-1}\,d^{-1}$.

Electrophysiology

Electrophysiological recordings were made from horizontal brain slices of 400-mm thickness. Brain tissue was cut using a Leica VT1000S microtome in oxygenated ice cold ACSF composed of (in mM): 130 NaCl, 2.5 KCl, 26 $NaHCO_3$, 1.25 NaH_2PO_4, 1.0 $CaCl_2$, 3.0 $MgCl_2$, and 10 D-glucose. After slicing, the tissue was maintained at a room temperature of 20~22°C for at least 60 min in ACSF of the same composition and then transferred to the recording chamber. Recordings were performed at room temperature of 20~22°C in oxygenated ACSF, contained (in mM): 130 NaCl, 2.5 KCl, 26 $NaHCO_3$, 1.25 NaH_2PO_4, 1.5 $CaCl_2$, 1.5 $MgCl_2$ and 10 D-glucose. Synaptic responses in dentate granule neurons were evoked by stimulation of lateral perforant path fibers applied at 0.1 Hz (100 μs duration) via a constant current isolation unit. Perforant path fibers were stimulated by placing a tungsten bipolar electrode in the outer half of the middle third dentate molecular layer. Evoked EPSPs were recorded using glass pipette electrodes (6~8 MΩ), filled with intracellular solution contained (in mM): 140 Cs-methanesulfonate, 8 NaCl, 1 $MgCl_2$, 0.5 EGTA, 10 HEPES, 7 phosphocreatine, di-(tris) salt, 4 Mg-ATP, 0.3 Na-GTP, 5 QX314 (pH 7.3 was adjusted with NMDG). The EPSC rise time was measured as the time from 10 to 90% peak amplitude. Whole-cell patch-clamp recordings were performed from DG granule neurons, visually identified with infrared video microscopy and differential interference contrast optics. Data were collected with a Multi-Clamp 700B amplifier (Molecular Devices, USA) using Clampex10.2 acquisition software (Molecular Devices, USA) and digitized with Digidata 1322A (Molecular Devices, USA). Raw data were low pass filtered at 4 kHz and collected for off-line analysis at a sampling rate of 10 kHz. Chemicals for ACSF and intracellular solutions were purchased from Sigma (USA).

RESULTS

To investigate the role of astrocytic GABA on the PP to DG granule neuron synaptic transmission, we assessed an effect of selegiline, an irreversible inhibitor that was demonstrated to

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block the production of GABA in astrocytes [7, 8]. Consistently, when administered to mouse in drinking water or acutely applied to hippocampal slices, selegiline decreased the amplitude of evoked excitatory post-synaptic currents (eEPSCs) in DG granule neurons, without altering the resting membrane potential, somatic input resistance, amplitudes of the action potentials and the

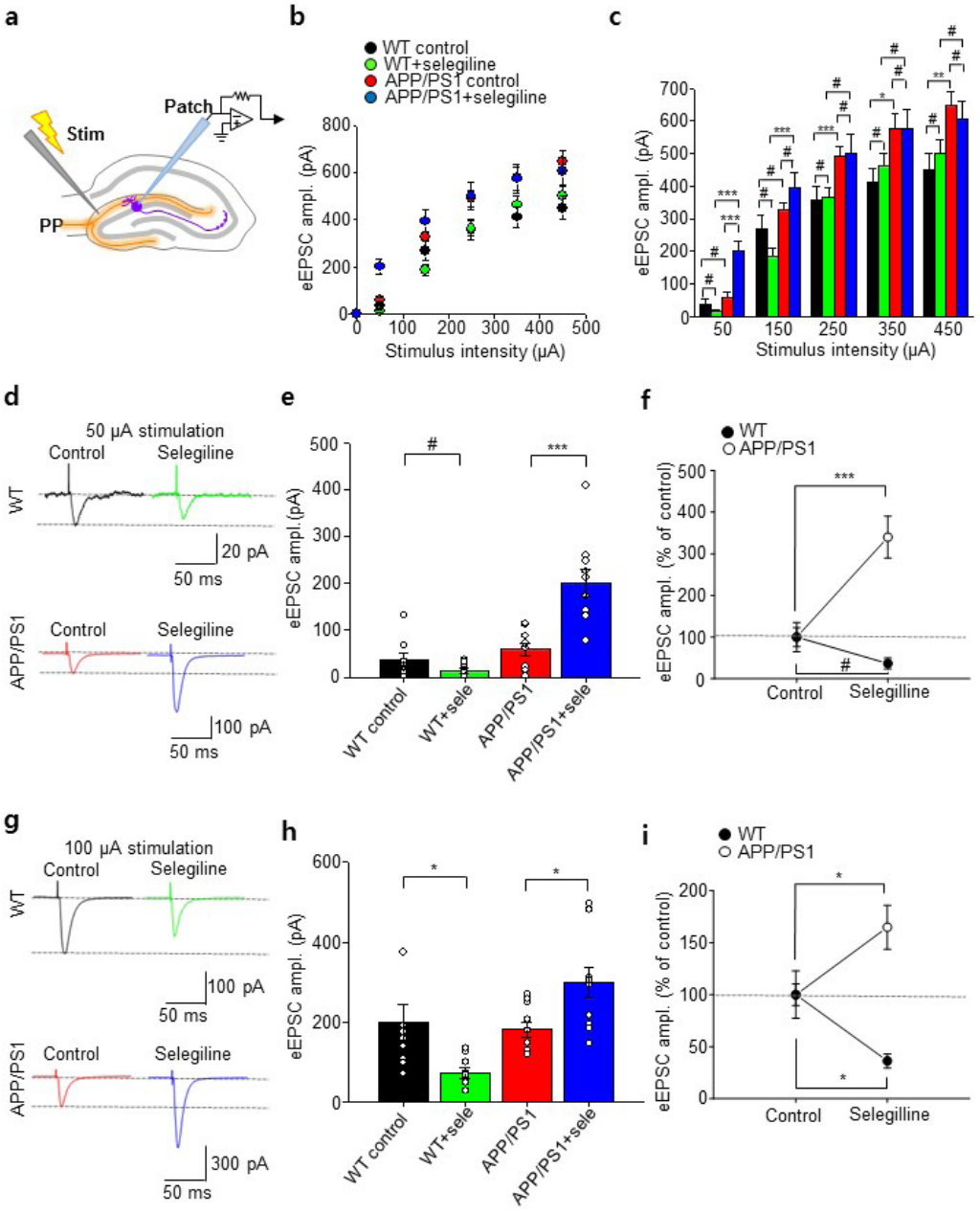

Fig. 1. Selegiline attenuates the amplitude of eEPSCs in DG granule neurons in WT mice but increases in APP/PS1 mice. (a) Schematic diagram of brain slice electrophysiology experiments. (b) The averaged amplitude values of eEPSCs plotted as a function of stimulus intensity (n=9 cells, 9 cells, 10 cells, and 10 cells for WT control, WT+selegiline, APP/PS1 control, and APP/PS1+selegiline, respectively). (c) Summarizing results for the amplitude of eEPSCs in WT and APP/PS1 mice. (d) Representative eEPSCs in control and selegiline-treated WT (*upper panel*) and APP/PS1 (*lower panel*) mice at 50 μA stimulation intensity of PP. (e) Summarizing results for absolute values of the amplitude of EPSCs evoked by 50 μA stimulation of PP in WT (9 cells) and APP/PS1 (10 cells) mice. (f) Summarizing results for normalized values of the amplitude of EPSCs in WT and APP/PS1 mice. (g) Representative eEPSCs in control and selegiline-treated WT (*upper panel*) and APP/PS1 (*lower panel*) mice at 100 μA stimulation intensity of PP. (h) Summarizing results for absolute values of the amplitude of EPSCs evoked by 100 μA stimulation of PP in WT (9 cells) and APP/PS1 (9 cells) mice. (i) Summarizing results for normalized values of the amplitude of EPSCs in WT and APP/PS1 mice. All data are represented as mean±S.E.M. (#non-significant, *p<0.05, **p<0.01, ***p<0.001, Student's unpaired t-test).

firing rate of granule neurons [8]. Mice were administered with selegiline for one week prior to electrophysiology experiments at a dosage sufficient to selectively inhibit MAOB over MAOA activity (see Materials and Methods). We have found that selegiline significantly reduced the amplitude of eEPSCs at 50 μA or 100 μA stimulation intensity in wild-type (WT) mice, whereas it significantly increased the eEPSC amplitude in APP/PS1 mice under the same stimulation conditions (Fig. 1b~i). These results imply an excitatory action of astrocytic GABA in WT mice and an inhibitory action in APP/PS1 mice.

The effects of astrocytic GABA on the amplitude of eEPSCs may result from a pre-synaptic action of GABA on the release probability at the PP terminals. To test an involvement of pre-synaptic mechanism to the observed phenomena, we estimated an effect of selegiline on paired pulse ratio (PPR) of two consecutively evoked EPSCs (50 ms apart) in WT and APP/PS1 mice. We found that selegiline did not change PPR in WT mice, whereas it significantly reduced PPR in APP/PS1 mice by about 15% (Fig. 2). These results suggest that astrocytic GABA does not change the release probability in WT mice, whereas it decreases the release probability in APP/PS1 mice. In other words, the astrocytic GABA tonically decreased the amplitude of eEPSCs in APP/PS1 mice via a pre-synaptic mechanism by inhibiting neurotransmitter release from PP terminals, whereas there was no involvement of pre-synaptic mechanism in WT mice.

Then how does astrocytic GABA enhance the amplitude of eEPSCs? To address this question, we performed pharmacological experiments using selective antagonists for $GABA_A$ and $GABA_B$. The results revealed that bicuculline did not change the amplitude of eEPSCs in WT mice (Fig. 3a and 3b), whereas it significantly increased the amplitude of eEPSCs in APP/PS1 mice (Fig. 3e and 3f). These results indicate that $GABA_A$ receptors are not involved in the excitatory action of astrocytic GABA in WT mice, whereas $GABA_A$ receptors mediate the inhibitory action of astrocytic GABA in APP/PS1 mice. GABA released from interneurons attenuates excitation of post-synaptic neurons by reducing dendritic input resistance (R_{in}) or by perisomatic inhibition [15, 16]. Then, attenuation of the interneuronal activity would result in an increase in dendritic R_{in} and subsequent increase in the rise time of eEPSCs in DG granule neurons. Consistent with the hypothesis about an involvement of interneurons in the suppressing effect of selegiline on eEPSC in WT mice, selegiline treatment significantly increased the rise time of eEPSC from 2.84±0.17 ms to 4.35±0.26 ms (Fig. 3g). Interestingly, the rise time of eEPSCs in DG granule neurons of APP/PS1 mice was not significantly altered by selegiline (Fig. 3h).

Next we examined the contribution of $GABA_B$ receptors in excitatory action of astrocytic GABA in WT mice. We estimated the effect of CGP55845, a $GABA_B$ receptor antagonist, on the amplitude of eEPSCs in the presence of bicuculline. We found that CGP55845 significantly attenuated the amplitude of eEPSC by about 45% (Fig. 3c and 3d) in the presence of bicuculline. The degree of reduction by CGP55845 was comparable to the degree of reduction by selegiline in the WT mice (Fig. 1i), indicating that $GABA_B$ receptor accounts for the most of the excitatory effect shown by astrocytic GABA.

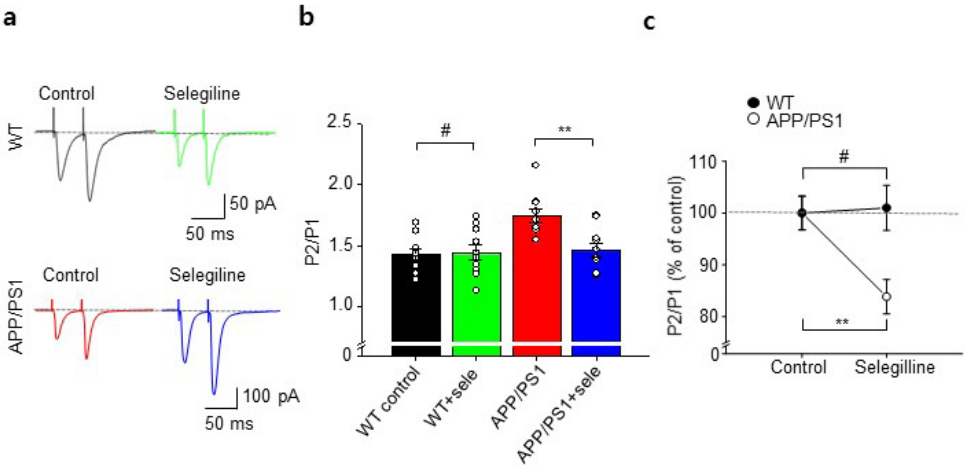

Fig. 2. Selegiline does not alter PPR in WT mice but reduces in APP/PS1 mice. (a) Representative traces of two subsequent EPSCs in control and selegiline-treated WT (*upper panel*) and APP/PS1 (*lower panel*) mice. (b) Summarizing results for absolute values of the PPR of EPSC in WT (9 cells) and APP/PS1 (10 cells) mice. (c) Summarizing results for normalized values of the PPR of EPSCs in WT and APP/PS1 mice. In all experiments EPSCs were evoked by 100 μA stimulation of PP. Inter-pulse interval was 50 ms. All data are represented as mean±S.E.M. (#non-significant, **p<0.01, Student's unpaired t-test).

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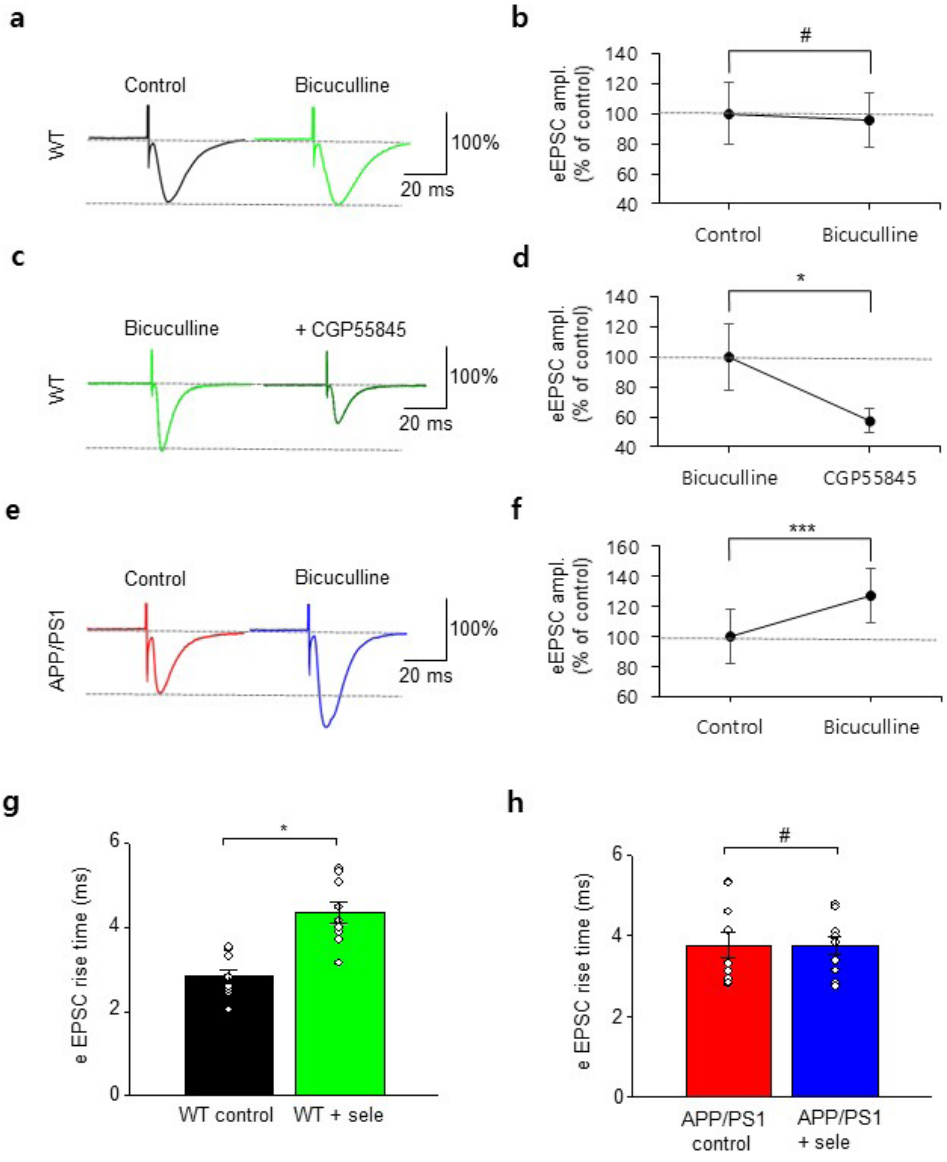

Fig. 3. Bicuculline and CGP55845 do not alter the amplitude of eEPSCs in WT mice but increases in APP/PS1 mice. (a) Representative eEPSCs before and after bath application of bicuculline in WT mice. (b) Summarizing results for effect of bicuculline on the amplitude of EPSCs in WT mice (9 cells). (c) Representative eEPSCs before and after bath application of CGP55845 in WT mice. (d) Summarizing results for effect of CGP55845 on the amplitude of EPSCs (4 cells). (e) Representative eEPSCs before and after bath application of bicuculline in APP/PS1 mice. (f) Summarizing results for effect of bicuculline on the amplitude of EPSCs in APP/PS1 mice (9 cells). Bicuculline was applied at a concentration of 10 μM. (g) The rise time of eEPSCs in control and selegiline-treated WT mice (9 cells) (h) The rise time of eEPSCs in control and selegiline-treated APP/PS1 (9 cells) mice. All data are represented as mean±S.E.M. (#non-significant, ***$p<0.001$, Student's paired t-test). In all experiments EPSCs were evoked by 100 μA stimulation of PP.

The excitatory role of $GABA_B$ receptor in WT mice and inhibitory role of $GABA_A$ in APP/PS1 mice were confirmed in PPR experiment using bicuculline and CGP55845. Similar to selegiline treatment, we found that bicuculline did not change PPR in WT mice (Fig. 4a and 4b), whereas it significantly decreased PPR in APP/PS1 mice by about 12% (Fig. 4e and 4f). These results and the similar degree of reduction in PPR by selegiline (Fig. 2c) in APP/PS1 mice indicate that presynaptic $GABA_A$ receptor at PP terminals is responsible for the inhibitory action of astrocytic GABA in APP/PS1 mice.

The observation that bicuculline did not alter PPR in WT mice (Fig. 4a and 4b) is intriguing because it excludes a possibility of involvement of presynaptic $GABA_A$ receptors at PP terminals. More interestingly, PPR was not significantly changed by CGP55845, again, eliminating the possibility of presynaptic $GABA_B$ receptors at PP terminals (Fig. 4c and 4d). Then where is the $GABA_B$ receptor that is responsible for the excitatory action of astrocytic GABA? The above results suggest that $GABA_B$ receptor is present at the presynaptic terminals of local interneurons which form a feed-forward inhibitory circuit of DG and that astrocytic GABA targets these $GABA_B$ receptors. Thus, the action of astrocytic GABA in WT mice is a tonic disinhibitory action on $GABA_B$ receptor of local interneurons of DG.

DISCUSSION

Attenuation of EPSC in DG granule neurons by selegiline in the present study reveals an excitatory action of astrocytic GABA

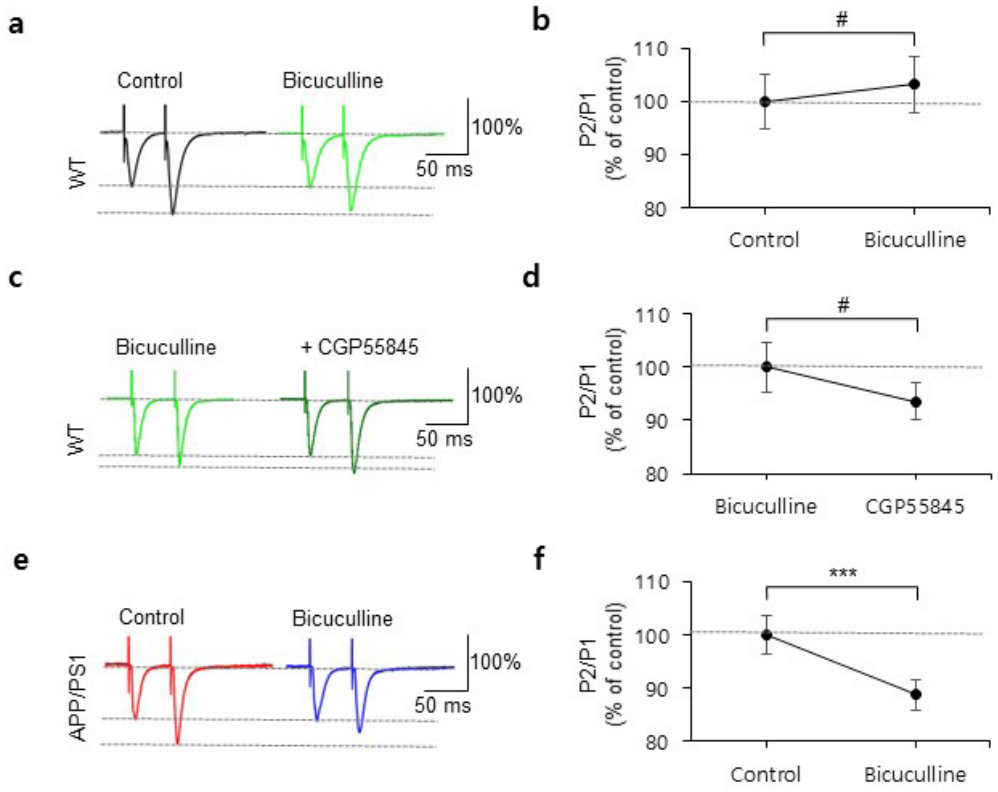

Fig. 4. Bicuculline and CGP55845 do not alter the PPR in WT mice but bicuculline reduces the PPR in APP/PS1 mice. (a) Representative traces of two subsequent EPSCs before and after bath application of bicuculline in WT mice. Inter-pulse interval was 50 ms. (b) Summarizing results for effect of bicuculline on the PPR of EPSCs in WT (9 cells). (c) Representative traces of two subsequent EPSCs before and after bath application of CGP55845 in WT mice. (d) Summarizing results for effect of CGP55845 on the PPR of EPSCs in WT mice. Bicuculline was applied at a concentration of 10 μM. (e) Representative traces of two subsequent EPSCs before and after bath application of bicuculline in APP/PS1 mice. Inter-pulse interval was 50 ms. (f) Summarizing results for effect of bicuculline on the PPR of EPSCs in APP/PS1 mice (9 cells). Bicuculline was applied at a concentration of 10 μM. Data are represented as mean±S.E.M. (#non-significant, ***p<0.001, Student's paired t-test). In all experiments EPSCs were evoked by 100 μA stimulation of PP. Inter-pulse interval was 50 ms.

at weak stimulations of PP fibers. The finding that selegiline did not alter PPR at PP to granule neuron synapse calls for a non-presynaptic target of astrocytic GABA. In addition, the positive effect by $GABA_B$ antagonist and negative effect by $GABA_A$ antagonist on eEPSC suggest that the target of astrocytic GABA is $GABA_B$ receptors, not $GABA_A$. DG granule neurons are known to express $GABA_B$ receptor sub-units on their dendrites in the outer molecular layer of DG [17, 18]. Therefore, it may appear that astrocytic GABA directly inhibits activity of DG granule neurons by targeting $GABA_B$ receptors on DG granule neurons. However, such a mechanism cannot explain why the effect of astrocytic GABA was observed only at relatively weak stimulations of PP fibers (Fig. 1b and 1c). Another possible target of astrocytic GABA is the $GABA_B$ receptors of interneurons. There is a subpopulation of hilar interneurons that project onto proximal dendrites and perisomatic regions of DG granule neurons [19]. Those interneurons receive direct input from PP to form feed-forward inhibitory circuit of DG, thus capable of indirectly modulating the PP to granule neuron transmission. Those interneurons have strong immunoreactivity for $GABA_B$ receptors in the inner molecular layer of DG [18]. It has been also reported that all hilar interneurons that project to the inner molecular layer of DG have a low activation threshold for PP stimulation compared to that of DG granule neurons [19]. Based on these previous reports and our results demonstrating that $GABA_B$ receptor antagonist attenuated the amplitude of eEPSCs in granule neurons, we conclude that astrocytic GABA targets $GABA_B$ receptors on the axonal terminals of hilar interneurons projecting to the proximal dendrites and perisomatic region of DG granule neurons. The lower PP stimulation threshold for the activation of hilar interneurons could be the reason for the presence of effect by $GABA_B$ antagonist only with a weak stimulation of the PP. Astrocytic GABA is tonically and negatively modulating synaptic GABA release in interneuronal terminals, thus reducing the inhibitory drive on

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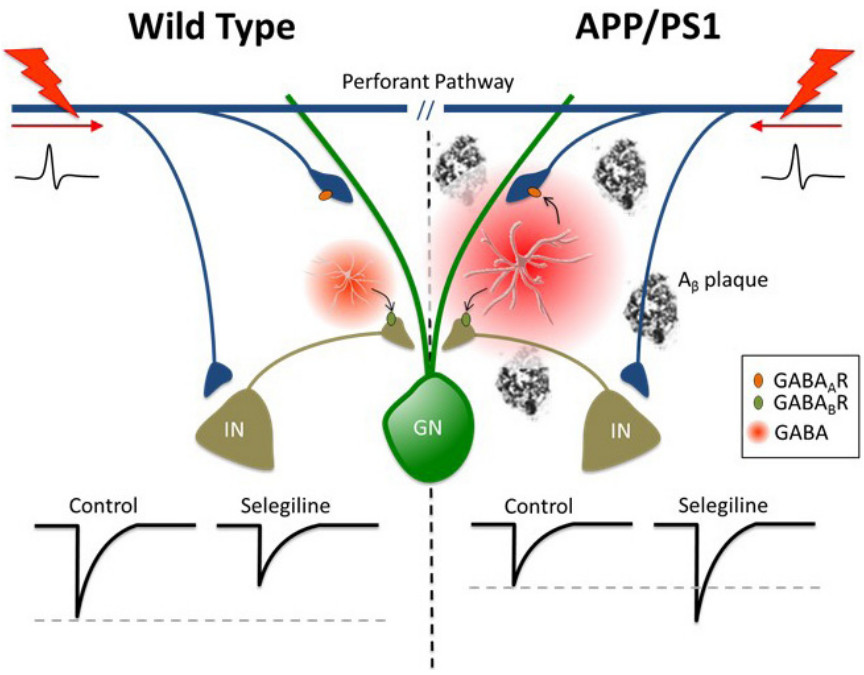

Fig. 5. Proposed mechanism of action of astrocytic GABA in regulation of PP to DG granule neuron synaptic transmission. Under normal conditions, GABA from astrocytes located in the molecular layer of DG, targets $GABA_B$ receptors on axonal terminals of hilar interneurons that project onto the proximal dendritic and the perisomatic regions of granule neurons. Activation of the interneuronal $GABA_B$ results in a decrease in transmitter release at interneuron to granule neuron synapse and hence disinhibits the granule neuron activity. In diseased DG of APP/PS1 mice, reactive astrocytes in molecular layer of DG have aberrantly elevated production and rates of release of GABA. This GABA activates $GABA_A$ receptors on PP to DG granule neuron terminals and reduces release probability in PP to granule neuron synapse, thus inhibiting PP to DG granule neuron synaptic transmission. IN, hillar interneuron; GN, granule neuron; A_β, beta-amyloid.

granule neurons in favor of excitatory drive from PP (Fig. 5). With increasing stimulation strength of PP, the proportion of inhibitory drive on granule neurons is relatively decreased compared to the direct excitatory drive from PP (Fig. 5). Under this condition, the astrocytic GABA appears to be confined to the inner molecular layer of DG. Future investigations are needed to explore the possible role of hilar interneurons in disinhibitory action of astrocytic GABA in WT mice.

In contrast to astrocytes in WT, reactive astrocytes in the molecular layer of DG in APP/PS1 mice have increased production and tonic release of GABA [8]. This more abundant astrocytic GABA can extend to more outer molecular layer of DG to affect presynaptic terminals of PP. Our results demonstrate that in APP/PS1 mice, GABA from reactive astrocytes targets $GABA_A$ receptors at the PP terminals to powerfully reduce the release probability of PP to DG granule neuron synapse (Fig. 5). This direct inhibitory action of astrocytic GABA targeting presynaptic $GABA_A$ receptors accounts for the majority of inhibitory action observed at this synapse, as evidenced by a similar degree of reduction of amplitude of eEPSCs and PPR between selegiline and bicuculline. These results should provide a useful target to alleviate memory impairment in Alzheimer's disease model. A precise molecular/cellular mechanisms underlying enhanced sensitivity of PP terminals in AD mice is not well understood. One possibility might be up-regulation of $GABA_A$ receptors in the perforant path terminals or alterations in expression of Na-K-Cl or K-Cl co-transporters in PP terminals of APP/PS1 mice. Other possibilities may include morphological reorganization of astrocytes during gliosis and increased production and secretion of GABA by reactive astrocytes leading to altered spatial and temporal factors in glia-neuron communication in the DG of Alzheimer's brain that strengthens an influence of astrocytic GABA on PP-to-DG granule neuron synapse.

In summary, we have found that at low intensity of PP fiber stimulation, astrocytic GABA exerts a disinhibitory effect on DG granule neurons by targeting presynaptic $GABA_B$ receptors of feed-forward inhibitory circuit in DG of WT mice. In APP/PS1 mice, astrocytic GABA extends its target to presynaptic $GABA_A$ receptors of PP terminals to powerfully reduce the release probability at the PP to DG granule neuron synapse.

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