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Differential Inhibitory Action of Taurine between Electrically Evoked Response and Low Mg^{++}-Induced Spontaneous Activity in the CA1 Area of the Rat Hippocampal Slices

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Although one of the major physiological functions of taurine(2-aminoethanesulfonic acid) is the inhibitory action on the central nervous system(CNS), the mechanism of taurine in controlling the neuronal excitation in the CNS has been in controversy. Electrically evoked pEPSP and spontaneous activity induced by the perfusion of low Mg^{++}-ACSF were recorded in the CA1 pyramidal cell layer of the hippocampal slice. To test the inhibitory effect of taurine on spontaneous responses, taurine was treated for 2 min at various concentrations(1 mM-10 mM). Taurine reduced the spontaneous activity by 22.2% at 1 mM, and 100% at 2 mM in low Mg^{++}-ACSF. Evoked response was induced by electrical stimulation of Schaffer collateral-commissural fibers. Taurine reduced the evoked response by 11.68% at 3 mM, and 24.25% at 5 mM. Even 20 mM of taurine reduced the evoked response only by 24 % after 5 min treatment. That is, the inhibitory efficacy was much higher in spontaneous activity than in evoked response. The $GABA_A$ receptor antagonist, 100 uM bicuculline, blocked the inhibitory action of taurine, while $GABA_B$ receptor antagonist, 700 uM phaclofen, did not. Taurine blocked the spontaneous activity in the presence of CNQX, and did not block the electrically evoked responce in the presence of APV. The results suggest that taurine causes hyperpolarization in the cell by binding to $GABA_A$ receptor and preferentially attenuates NMDA receptor-mediated hyperexcitation, leaving synaptic transmission unmodified.

Key Words: Taurine, Hippocampus, CA1, GABA, NMDA

INTRODUCTION

Taurine, 2-aminoethanesulfonic acid, is a bioactive amino acid present in high concentrations in the mammalian brain and the levels vary significantly with brain area. Higher levels of taurine were found in cerebral cortex and hippocampus compared to brain stem and spinal cord (Lombardini, 1976). When taurine was initially found, its role was proposed as an inhibitory neurotransmitter in the central nervous system like GABA. In fact, exogeneous application of taurine causes hyperpolarizing currents in neurons and inhibits neuronal firing in various brain areas by increasing chloride ion permeability (Krnjevic & Pull, 1976; Oja & Kontro, 1978; Taber et al, 1986). Immunocytochemical study showed that taurine is distributed on soma, dendrites, axon, and synaptic terminals of neurons (Ottersen et al, 1985; Trop et al, 1992) and high affinity uptake into synaptic terminals has been demonstrated in cerebral cortex (Schmid et al, 1975; Lombardini, 1978; Wheler et al, 1981). However, despite its inhibitory action mediated via the increase in the Cl^- conductance, any attempt to identify taurine-specific receptor has not been successful so far. Previous studies showed that it exerts its action via $GABA_A$ receptor in cortex and hippocampus (Okamoto & Sakai, 1981; Galarreta et al, 1996), and glycine receptor in brain stem (Haas & Hosli, 1973), spinal cord (Mathers et al, 1989) and

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substantia nigra (Hausser et al, 1992). It also interacts with benzodiazepine binding site of $GABA_A$ receptor complex (Medina & DeRobertis, 1984; Willow & Padjen, 1986) and even lipid in cell membrane (Kontro & Oja, 1987). Furthermore, taurine synthetic enzyme, cysteine sulfonic acid decarboxylase (CSAD) was mostly seen in soma and dendrite, raising the possiblity that taurine is not a neurotransmitter, but rather acts as a neuromodulator. Due to its apparent inhibitory action on neural activity, the possibility of anticonvulsant role has been studied (Durelli & Mutani, 1983; Oja & Kontro, 1983; Toth et al, 1983). Though taurine was effective in reducing seizure activity in some genetically and experimentally induced animal models of seizure, it turned out to be unable to diffuse into the brain across blood brain barrier (Durelli & Mutani, 1983). Thereafter, the inhibitory action of taurine was rarely studied, and several studies demonstrated that taurine possesses many distinct actions from those of GABA, such as survival of neuronal cells (Huxtable, 1992; Felipo et al, 1993) and regulation of osmolarity (Wade et al, 1988).

Very recently it has been shown by Solís and his colleagues that inhibitory action of taurine was counteracted by $GABA_A$ receptor antagonist in the hippocampal slices where high concentration of taurine is distributed (Galarreta et al, 1996). However, the taurine concentration used to elicit inhibitory action was very high, compared to Taber et al's study in which 1~2 mM taurine perfusion for short period was enough to induce hyperpolarizing currents and inhibited spontaneously occuring action potentials (Taber et al, 1986). In Solís's study, treatment of 10 mM taurine for 15 min reduced only 30% of pEPSPs recorded in CA1 area of the hippocampal slices (Galarreta et al, 1996). It is generally accepted that the physiological concentration of taurine in the central nervous system ranges from 2 to 8 mM in the cell (Bernadi et al, 1984). Because the concentration of taurine demonstrating the inhibitory action on pEPSPs, one of criteria of synaptic trasmission, in *in vitro* experimental conditions was greater than physiological concentration, the physiological meaning of taurine-mediated inhibition became doubtful, at least in the hippocampus. In this study, we made an attempt to evaluate the physiological significance of taurine-induced inhibitory action using extracellular recording in the hippocampal slices. For this purpose, modification of pEPSP evoked by electrical stimulus and spontaneous activity developed during the perfusion with low Mg^{++}-ACSF were studied in the presence of taurine.

METHODS

Preparation of the hippocampal slice

Experiments were performed in transverse hippocampal slices (400~450 uM thick), obtained from adult Sprague Dawly rats (150~200 g), by standard procedures. Rats were decapitated under ether anesthesia. After the rat was decapitated, its brain was rapidly removed and dropped into ice-cold normal ACSF (in mM): NaCl 125.3, KCl 3, KH_2PO_4 1.4, $CaCl_2 \cdot H_2O$ 1.8, $MgSO_4$ 1.3, $NaHCO_3$ 23 and glucose 10, which was vigorously bubbled with 95% O_2/5% CO_2. The hippocampus was isolated by rolling it out from the surrounding cortex with a blunt spatula and was sliced by a McILWAIN-type tissue chopper. Slices were incubated in a holding chamber containing normal ACSF bubbled with gas mixture at 30°C. After allowing at least 1 hour recovery, a slice was transferred to a submersion-type recording chamber, continuously perfused with ACSF at 30°C equilibrated with a gas mixture.

Extracellular field potential (pEPSP) recording

To obtain evoked responses in the CA1 area, Schaffer collateral-commissural fibers were stimulated with electrical pulses (200~400 uA, 0.1 msec) using bipolar insulated tungsten electrodes. Stimulating electrode was located in stratum radiatum and electrical pulse was applied through stimulus isolator by a pulse generator every 30 sec. Extracellular field potentials (pEPSPs) from the stratum radiatum of the CA1 region were recorded in normal ACSF. Recording micropipettes were connected to field effect resistors, the outputs of which were filtered between 1 and 1000 Hz and amplified by WPI amplifier (DAM 80). To induce spontaneous activity, individual slices were pre-exposed to $MgSO_4$-omitted ACSF (low Mg^{++}-ACSF) prior to recording. Slices were incubated for more than 30 min in low Mg^{++}-ACSF before recording. Throughout experiments, recordings were carried out in the chamber perfused with low Mg^{++}-ACSF.

Drug application

All drug solutions were freshly prepared daily. Drugs were applied by addition to perfusion solution. Drug concentrations were as following: taurine (Sigma, St. Louis, MO), 1～150 mM; D-2-amino-5- phosphonovaleric acid (APV), 25 uM; 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), 20 uM; bicuculline (BIC), 100 uM; phaclofen, 700 uM. APV, CNQX, BIC, and phaclofen were purchased from Research Biochemicals Inc. (Natick, MA). The composition of normal ACSF was not modified during treatment of taurine because taurine itself didn't influence ionic balance of ACSF.

Data analysis

All data were stored on VCR tape and analyzed by measuring amplitudes before and after drug treatments. All data were expressed as mean±standard error unless otherwise specified. Statistical differences were assessed by one-way analyses of variance and two-tailed Student's *t* test.

RESULTS

To test action of taurine, extracellular field potentials were recorded in the CA1 pyramidal layer in response to electrical stimulation on Schaffer collaterals in the hippocampal slices. The action of taurine on neuronal activity was inhibitory as it has been reported (Krnjevic & Pull, 1976; Oja & Kontro, 1978; Taber et al, 1986). Perfusion with various concentraions of taurine for 2～5 min reduced electrically evoked field potentials by 10～60% in a dose dependent manner (Fig. 1). Its inhibitory effects reached the steady state at concentration of 50 mM with 60% reduction of pEPSPs. In our experiments, complete reduction of the pEPSP was never achieved even by 150 mM taurine. During washout, pEPSP increased gradually and recovered up to 90% over control values in about 10 min after termination of taurine. Though the recovered value tended to be larger than control, no statistical significance was obtained. Even after the treatment of 150 mM of taurine the recovery was shown within 10 min of washout, which indicated that the abrupt increase of osmolarity of ACSF due to high concentration of taurine didn't cause neural cell damages.

To further study whether high dose of taurine is required for the inhibition of neural activity, spontaneous activity was induced by the perfusion of low Mg^{++}-ACSF, and recorded in the CA1 area using extracellular recording. Low Mg^{++}-ACSF is known to elicit spontaneous activity by increasing neurotransmitter release and removing the block that Mg^{++} ions exert on the NMDA receptor. Spontaneous activity began to appear 20～30 min after incubation with low Mg^{++}-ACSF, and was continued without modification of response pattern in the course of perfusion with low Mg^{++}-ACSF so that it was easy to follow any changes in the amplitude of pEPSP caused by taurine. No rhythmic bursting activity with particular frequency was developed. Rather, spontaneous activity was like random repetitive firing of single field potentials with stable amplitude. The frequency of firings ranged from 1 to 10 Hz. Taurine inhibited spontaneous discharge generated in low Mg^{++}-ACSF in a dose-dependent manner as evoked response. Dose-response curve showed that the inhibitory efficacy was much higher in spontaneous activity than in evoked response (Fig. 1). Treatment of 3 mM taurine for 2 min was sufficient to completely block spontaneous activities developed during perfusion of low Mg^{++}-ACSF, at which concenrtation electrically evoked response was reduced only by 10% (n=4). Recovery was observed in 5 min after washout. The inhibitory effect of taurine on evoked response was reported to be mediated through $GABA_A$ receptor. To test whether this is the case in the spontaneous activity, $GABA_A$ receptor antagonist, bicuculline (BIC), or $GABA_B$ receptor antagonist, phaclofen, was pretreated before taurine application. When 100 uM BIC was present in the bath, no inhibitory effect of taurine was observed. Fig. 2 showed that even 10 mM taurine, which was well above the dose resulting in the complete reduction of spontaneous activity, did not inhibit the activity in the presence of BIC. Although taurine has been shown to bind to $GABA_B$ receptor (Kontro & Oja, 1990), pretreatment of 700 uM phaclofen did not counteract the inhibitory action of taurine, suggesting that the inhibitory effect on spontaneous activity was also mediated through $GABA_A$ receptor as shown in electrically evoked response.

Glutamate receptors are classified into NMDA receptors and AMPA receptors, depending on their

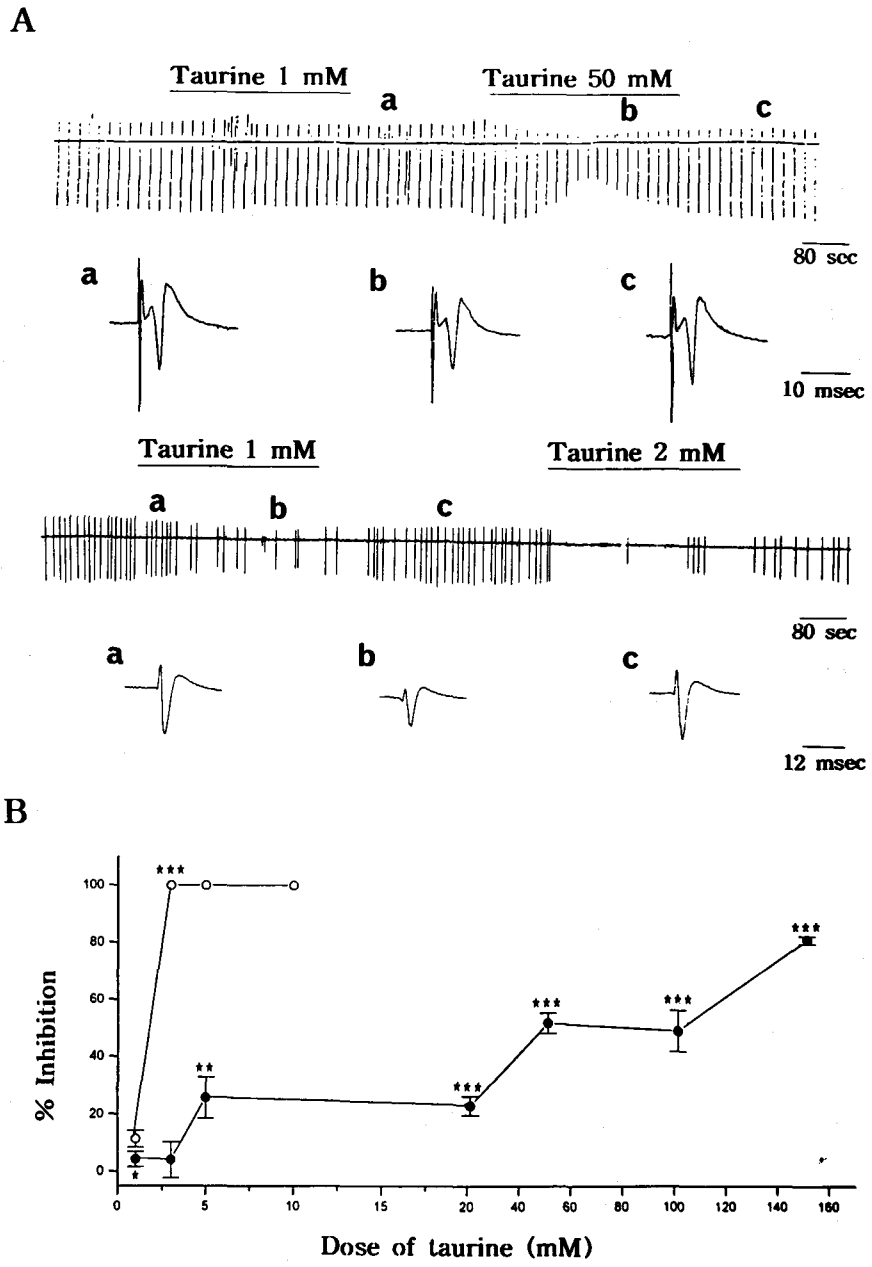
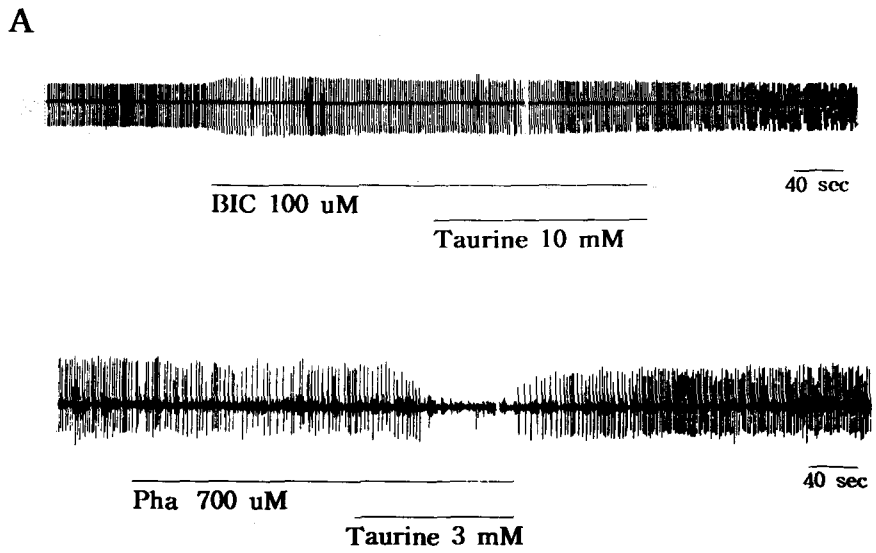


Fig. 1. Differential inhibitory action of taurine in spontaneous activities and electrically evoked responses.

A. Chart recordings of pEPSPs of evoked responses in the CA1 area by repetitive electrical stimulation of the Schaffer collaterals of hippocampal slice in a normal, Mg^{++}-containing medium (upper trace) and spontaneous activities from a slice in a medium containing no added Mg^{++} (low trace).

B. Dose-response curve of inhibitory action of taurine on spontaneous activity in low Mg^{++}-ACSF (open circle) and electrically evoked response (closed circle). % inhibition was calculated by dividing the amplitude after taurine treatment by control amplitude, then multifying 100. Statistical significances of inhibitory action are expressed by asterisks (*$p<0.05$; **$p<0.01$; ***$p<0.001$), compared to spontaneous activity/electrical activity. Values are mean±S.E.M. (n=3-8 per group).



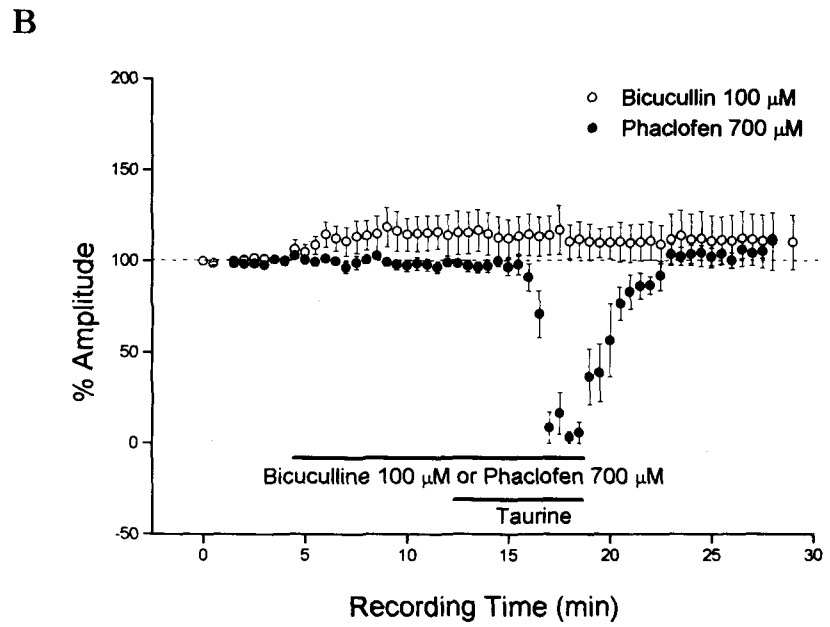


Fig. 2. The effect of GABA receptor antagonists on inhibitory action of taurine in spontaneous activity.

A. Representive sample chart recordings illustrating response to taurine application following 100 uM bicuculline(BIC) and 700 uM phaclofen(Pha). $GABA_A$ receptor antagonist, bicuculline 100 uM, abolished the inhibitory effect of taurine (upper trace), but $GABA_B$ receptor antagonist, phaclofen 700 uM, did not (low trace).

B. Time course of changes in amplitude. % amplitude is the percentage to control amplitude. Each calculation was made every 30 sec. Values represent mean±S.E.M. of 4 slices from each group.

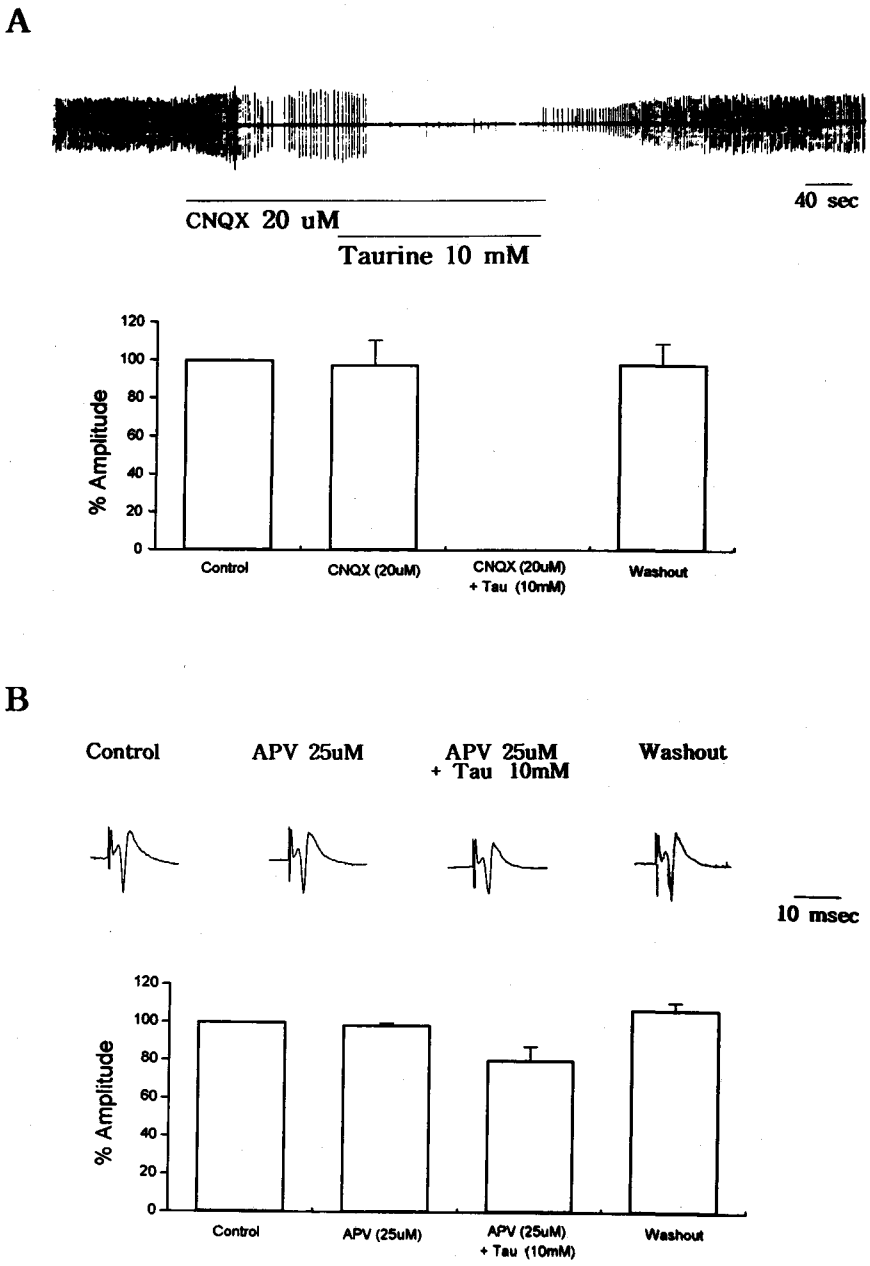


Fig. 3. Preferential effect of taurine to NMDA receptor-mediated response.

A. Representative chart recording comparing the effects of CNQX and taurine on spontaneous activity. Taurine inhibited spontaneous activity in the presense of non-NMDA receptor antagonist, 20 uM CNQX.

B. Single traces illustrating the effect of APV, CNQX, and taurine on electrically evoked response. Unlike the spontaneous activity, electrically evoked responses are mainly mediated through non-NMDA receptors. Each bar represents the mean $\pm$ S.E.M. (n=4).

affinity to specific agonists. It has been thought that single electrical stimulation delivered at low frequency activates non-NMDA receptors with some exceptions. We tried to test the possibility that the differential inhibitory effects between electrically evoked response and spontaneous activity in low Mg^{++}-ACSF are attributed to the differential involvement of NMDA receptors. For this purpose, APV and CNQX was pretreated to block NMDA receptor and non-NMDA receptor, respectively. Spontaneous activity was completely abolished by the 25 uM APV, while only slightly reduced by 20 uM CNQX, demonstrating that spontaneous activity is mediated via NMDA receptor in our preparation (Fig. 3). The remaining activity in the presence of CNQX was completely inhibited by further treatment with 10 mM taurine. Meanwhile, electrically evoked response was only slightly changed by 25 uM APV, indicating that it is mainly mediated via non-NMDA receptors. The inhibitory effect of taurine was marginal in the evoked response in cotreatment of APV and taurine. The degree of inhibition by 10 mM taurine in the presence of APV was 19%, which was consistent with the result reported in the evoked response in the absence of APV.

DISCUSSION

Our present study showed that taurine inhibited the neuronal activity via $GABA_A$ receptor in a dose dependent manner. The inhibitory effect of taurine on neuronal activity has been reported since it was discovered. Recently, it has been shown that when the effect of taurine on the electrically evoked pEPSPs was tested in the rat hippocampal slice, the degree of inhibition was very low with only 30% reduction of amplitude for 15 min treatment (Galarreta et al, 1996). Our results were compatible with Galarreta's report in that 3 min treatment of 10 mM taurine reduced pEPSPs by 10% and even 150 mM of taurine suppressed response only 40%, raising the possibility that the inhibitory effect of taurine may be functionally negligible in the CNS under physiological conditions. Though the concentration of taurine is mM level, the highest only after glutamate in the CNS, it is hardly expected to accumulate and remain in extracellular space in concentrations close to 10 mM, given that the concentration of glutamate is about 20 mM even in synaptic vesicle. One of the puzzling properties of taurine is that it can act at two distinct membrane receptors to produce inhibitory action. The taurine-induced inhibition has been known to be counteracted by different receptor antagonist depending on the brain area. Taurine-induced inhibition is unaffected by GABA receptor antagonist, but blocked by glycine receptor antagonist, strychnine, in the brain-stem, spinal cord, and substantia nigra. Recently, using whole cell patch clamp technique, it has been demonstrated that taurine from 100 uM to 1 mM opens chloride-channel in spinal ganglionic cells and cortical cells which are antagonized by strychnine and bicuculline, respectively. Galarreta's and this present study showed that taurine action is blocked by bicuculline in the hippocampus.

In the other hand, under more physiologically feasible concentrations, spontanenous activity developed during perfusion of low Mg^{++}-ACSF was effectively decreased by taurine. Our study leads to conclude that the preferential inhibition of spontaneous activity is attributable to the NMDA receptors which are activated during the perfusion of low Mg^{++}-ACSF. It has been well documented that reduction of Mg^{++} in ACSF enhances synaptically evoked potentials and facilitates the generation of repetitive discharge (Coan & Colliridge, 1985). Large spontaneous depolarizations were also reported in neocortical cells when Mg^{++} was omitted from ACSF (Thomson, 1985; Avoli et al, 1991). These effects could be blocked by 2-APV, indicating the involvement of NMDA receptors (Davies & Watkins, 1979). The activation of NMDA receptors in low Mg^{++}-ACSF is further supported by the present results showing the complete reduction of spontaneous activity by APV, but the slight suppresion by CNQX. Meanwhile, electrically evoked activity was largely suppressed by CNQX, not by APV. The result that taurine blocked the spontaneous activity in the presence of CNQX and didn't block the electrically evoked response in the presence of APV demonstrated the preferential effect of taurine. These results suggest that taurine preferentially attenuates NMDA receptor-mediated hyperexcitation, which is related to seizure and excitotoxicity, while leaving synaptic transmission unmodified.

Interaction of NMDA receptors with taurine has been reported in several studies. Activation of NMDA receptors causes an increase in extracelluar taurine levels in various brain regions both *in vivo*

and *in vitro* (Lehmann et al, 1984. 1985a, b; Magnusson et al, 1991; Menendez et al, 1989, 1990, 1993). Although taurine release induced by various stimuli, including activation of non-NMDA receptors, is mainly due to cellular swelling, the release of taurine caused by NMDA treatment seems to be triggered by mechanisms other than swelling, since it is insensitive to extracellular osmorality (Menendez et al, 1990; Shibanoki et al, 1993). It has been reported that release of taurine is primarily dependent on excessive concentration of excitatory amino acids, suggesting that taurine may not be released during normal synaptic transmission, but only as a result to cell damage (Lehmann et al, 1984, Magnusson et al, 1991). Based on the preferential inhibitory action of taurine observed here, we postulate that the increase of the extracellular taurine level following overactivation of NMDA receptors may well serve as a neuromodulator that protects against cell damage, a function that differs from its established osmoregulatory role. Since our results indicate that $GABA_A$ receptor activation is engaged in the inhibitory action of taurine, a possible mechanism we propose is that taurine causes hyperpolarization in the cell by binding to $GABA_A$ receptor, which eventually shunts NMDA receptor-mediated excitation.

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