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Taurine-evoked chloride current and its potentiation by intracellular Ca^{2+} in immature rat hippocampal CA1 neurons

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Summary. Taurine is one of the most abundant free amino acids in the immature mammalian central nervous system. In the present study, whole-cell patch-clamp recordings were made to examine taurine-evoked currents (I_{Tau}) in acutely dissociated immature rat hippocampal CA1 neurons. Taurine at low concentrations ($\leq$1 mM) activated glycine receptors while at high concentrations ($\geq$3 mM) activated both glycine and $GABA_A$ receptors. Moreover, elevation of intracellular Ca^{2+} via non-NMDA receptor activation enhanced I_{Tau} reversibly.

The results indicate that taurine may act as a native ligand of glycine receptors and modulate neurotransmissions in the immature hippocampus, and under certain conditions it can also activate $GABA_A$ receptors. The potentiation of I_{Tau} by intracellular Ca^{2+} may contribute to the protection effect of taurine under some cell-damaging conditions.

Keywords: Taurine – Glycine receptors – $GABA_A$ receptors – Intracellular Ca^{2+}

Introduction

Taurine (H_2N-CH_2-CH_2-SO_3H) is one of the most abundant free amino acids in the mammalian central nervous system (CNS), and its concentration even exceeds that of glutamate during neural development (Sturman, 1993). The structural simplicity of this β-amino acid belies the complexity of its biological actions. These are many and varied, both within and outside of the CNS (reviews: Huxtable, 1989, 1992). It is well known that the abundant taurine in the hippocampus possesses neuroprotective effects: protecting neuronal cells from excitotoxity (French et al., 1986), improving the recovery of neuronal function following cerebral hypoxia (Schurr et al., 1987) and antagonizing the calcium overload (Zhao et al., 1999). Under cell-damaging conditions (such as ischemia, free radicals and metabolic poisons), the release of taurine was remarkably enhanced in both adult and developing hippocampus (Saransaari and Oja, 2000a, b). The mechanisms of these protective effects are complex and appear to be related with not only osmoregulatory but also some other actions such as neuroinhibitory actions.

There are numerous reports of the neuroinhibitory actions of taurine, dating from the findings of Curtis and colleagues (Cutis and Watkins, 1960, 1965; Curtis et al., 1968). In the hippocampus, taurine could inhibit the firing of pyramidal neurons by increasing membrane chloride conductance and causing hyperpolarization (Taber et al., 1986). On the basis of antagonist studies, Curtis divided neuroinhibitory amino acids into two classes, glycine-like and GABA-like, and taurine fell into both classes and depended on the system studies (Curtis et al., 1968, 1971). More recently, Olmo et al. (2000) reported that taurine activated $GABA_A$ receptors in the adult rat hippocampus, and Mori et al. (2002) found that endogenous taurine could activate glycine receptors in cultured rat hippocampal slices.

During the early development of hippocampus, the concentration of taurine (Sturman, 1993) decreased and the subunits of neurotransmitter receptors changed significantly (Malosio et al., 1991; Laurie et al., 1992). In the present study, using whole-cell patch-clamp recordings, the receptor mechanism of taurine-evoked whole cell currents (I_{Tau}) was examined in acutely dissociated immature rat hippocampal

CA1 neurons. And as the elevation of intracellular Ca^{2+} occurs under some cell-damaging conditions, we also examined its modulation on I_{Tau} to study the mechanism of the protective effect of taurine.

Material and methods

Isolation of neurons

The care and use of animals and the experimental protocol of this study were approved by the Institutional Care and Use Committee at University of Science and Technology of China. We performed experiments on CA1 neurons prepared as described by Li et al. (2002). Briefly, Wistar rats (14–16 days) were anaesthetized with pentobarbitone sodium (45–50 mg/kg, i.p.). The animals were then decapitated and the brains were quickly excised and placed into an ice-cold incubation solution. The brains were then glued to the chilled stage of a vibrotome tissue slicer [VT1000S, Leica instruments Ltd, Wetzlar, Germany] with iced incubation solution and sectioned to a thickness of 400 μm. Slices were preincubated in the incubation solution for 0.5–1.0 hour at room temperature (22–25°C) and then were transferred to well-oxygenated standard external solution containing 1 mg pronase/6 ml and incubated for 20 min at 31°C. After an additional 20 min incubation in 1 mg thermolysine/6 ml at the same temperature, micropunches of the hippocampal CA1 region were isolated and transferred to a 35 mm culture dish (Falcon) filled with standard external solution. Under visual guidance under a phase contrast microscope [IX70, Olympus Optical Co., Ltd, Tokyo, Japan], mild trituration of these tissue punches through heat-polished glass pipettes of progressively smaller tip diameter was served to dissociate single neurons. Within 20 min of deposition, isolated neurons had attached to the bottom of the culture dish and were ready for electrophysiological experiments.

Solutions and drugs

The ionic composition of the incubation solution was (mM): 124 NaCl, 24 $NaHCO_3$, 5 KCl, 1.2 KH_2PO_4, 2.4 $CaCl_2$, 1.3 $MgSO_4$, 10 glucose, aerated with 95% O_2/5% CO_2 to a final pH of 7.4. The standard external solution contained (mM): 150 NaCl, 5 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 10 N-hydroxyethylpiperazine-N′-2-ethanesulphonic acid (HEPES), and 10 glucose. The pH was adjusted to 7.4 with Tris-hydroxymethyl aminomethane (Tris-base). When measuring the current-voltage relationship of taurine-evoked currents, 0.3 μM tetrodotoxin and 0.2 mM $CdCl_2$ were used to block sodium channels and voltage dependent Ca^{2+} channels. $CdCl_2$ had no noticeable effect on the I_{Tau} at the concentration used. The Ca^{2+}-free extracellular solution was prepared by the omission of $CaCl_2$ and the addition of 2 mM $MgCl_2$. The osmolarity of all bath solutions was adjusted to 325–330 mOsm/L with sucrose (3300, Norwood, Massachusetts, USA).

The patch pipette solution for whole-cell patch recording was (mM): 120 CsCl, 20 TEA-Cl, 2 $MgCl_2$, 1 $CaCl_2$, 10 EGTA, 2 Na_2ATP, 10 HEPES. The internal solutions were adjusted to a pH of 7.2 with Tris-base.

Drugs used in the present experiments were purchased from Sigma. Drugs were first dissolved in ion-free water and then diluted to the final concentrations in the standard external solution just before use or dissolved directly in the standard external solution. Drugs were applied using a rapid application technique termed the "Y-tube" method throughout the experiments (Xu et al., 1996). This system allows a complete exchange of external solution surrounding a neuron within 20 ms.

Electrophysiological recording and data analysis

The electrophysiological recordings were performed in conventional whole-cell patch recording configurations under voltage-clamp conditions. Patch pipettes were pulled from glass capillaries with an outer diameter of 1.5 mm on a two-stage puller [PP-830, Narishige Co., Ltd, Tokyo, Japan]. The resistance between the recording electrode filled with pipette solution and the reference electrode was 4–6 MΩ. Membrane currents were measured using a patch-clamp amplifier [200 B, Axon Instruments, Foster City, CA, USA], sampled and analyzed using a DigiData 1320 A interface and a computer with the pCLAMP system [Version 8.0, Axon Instruments]. In most experiments, 70–90% series resistance was compensated. The holding potential was −50 mV throughout the experiment, except when I–V relationships were examined. All the experiments were carried out at room temperature (22–25°C).

Clampfit software was used for data analysis. All values represented the mean ± standard error of the mean. Statistical comparison was carried out by using Student's t test with $p < 0.05$ considered significant.

Results

Taurine responses in immature hippocampal CA1 neurons

The application of taurine evoked inward currents in all acutely dissociated hippocampal CA1 neurons was tested (n = 150, Fig. 1A). In general, the taurine-evoked currents (I_{Tau}) became detectable at a concentration of about 0.1 mM and then increased with the concentration increased. It seems that we didn't get the maximal taurine response when tested with 30 mM agonist (Fig. 1B). As intracellular and extracellular concentrations of taurine are generally in mM and μM ranges respectively in the hippocampus (Huxtable, 1989), we did not employ higher concentration of agonist. The amplitude of I_{Tau} varied significantly between neurons. For 1 mM taurine, current amplitudes were 236.6 ± 43.7 pA (n = 40) and ranged from zero to several nA.

Low-level taurine only activates glycine receptors whereas high-level taurine can activate both glycine and $GABA_A$ receptors

The current-voltage relationship of I_{Tau} was studied, and the results indicated that I_{Tau} was a chloride current. Figure 2A shows examples of the voltage-ramp protocol applied to measure the reversal potential (E_{Tau}) of I_{Tau}. The E_{Tau} was – 2.8 ± 0.4 mV (n = 5) and −2.9 ± 0.5 mV (n = 5) for 1 and 10 mM taurine, respectively. They were both close to the theoretical Cl^- equilibrium potential of −2.5 mV calculated with the Nernst equation in the present experimental

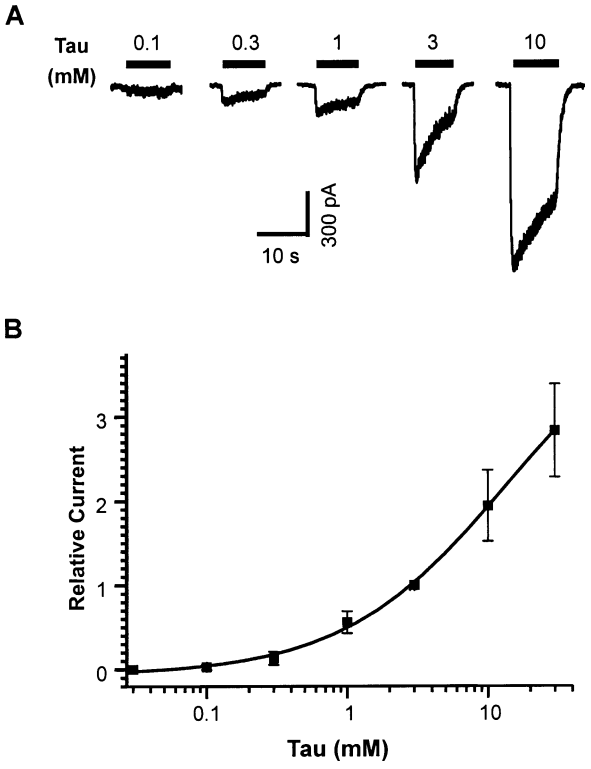

Fig. 1. Taurine (*Tau*) responses in immature hippocampal CA1 pyramidal neurons. **A** Inward currents induced by Tau at various concentrations. **B** Concentration-response relationship for taurine-activated currents (I_{Tau}). All currents were normalized to the peak current amplitude induced by 3 mM Tau(*). Each point represents the mean of six neurons. In all figures the vertical bars show mean ± S.E.M

conditions of 161 and 146 mM Cl^- in the external and internal solutions, respectively (Fig. 2C).

Previous studies showed that taurine can activate both glycine and $GABA_A$ receptors in rat supraoptic magnocellular neurons and basolateral amygdala neurons (Hussy et al., 1997; McCool and Botting, 2000). Here in hippocampal neurons we studied the pharmacological properties of I_{Tau} with the selective glycine receptor antagonist strychnine (Str) and $GABA_A$ receptor antagonist bicuculline (Bic).

At low-concentrations ($\leq$1 mM), I_{Tau} was almost fully inhibited by Str (1 μM), but was unaffected by Bic (10 μM). The neurons showing no response to glycine (0.1 mM) also exhibited no response to low-levels of taurine and vice versa (n = 10). These results indicate that low-levels of taurine activate glycine receptors only.

At high-concentrations ($\geq$3 mM), I_{Tau} was partly inhibited by either Str (3–30 μM) or Bic (10–30 μM), and was almost completely inhibited by co-application of both antagonists. But from this pharmacological experiment we can only get the ratios of current components through glycine receptors (I_{Gly}) and GABA receptors (I_{GABA}) approximatively (discussed later). In Fig. 3 the ratio of I_{GABA} component increased significantly as the concentration of agonist increased. This indicates that high-levels of taurine activate both glycine and $GABA_A$ receptors.

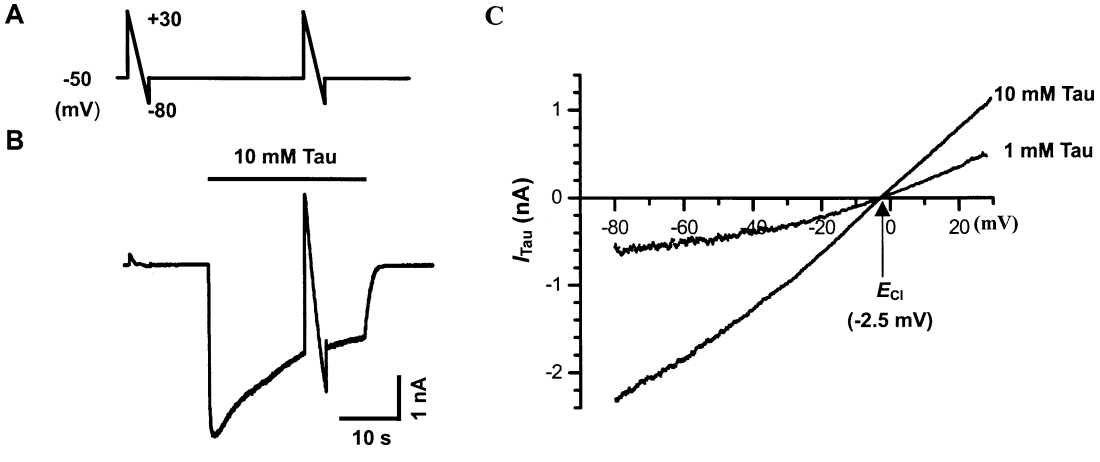

Fig. 2. The current-voltage relationship of I_{Tau} studied with a votage-ramp protocol. **A** A pair of voltage-ramps ranging from +30 to −80 mV was applied to the neurons at a rate of 1 mV/10 ms. Tau was applied to the cell and covered the second ramp of each pair. Traces obtained from the first ramp measured background or leakage currents. The I–V curve was produced by subtracted the trace elicited by the first ramp from that elicited by the second ramp. **B** Typical I_{Tau} recorded with 10 mM Tau by using the voltage-ramp protocol. **C** Current-voltage curves derived from one neuron with different concentrations of Tau (one curve was just derived from **B**)

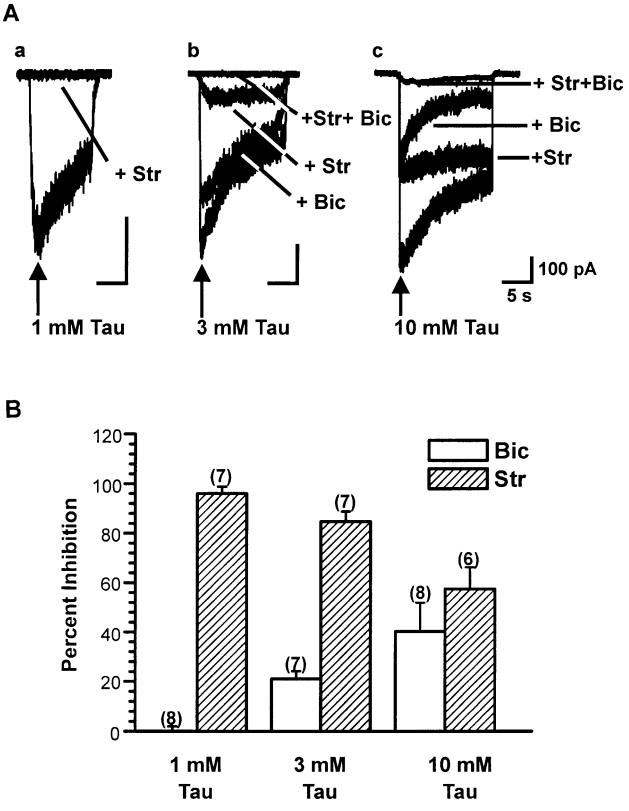

Fig. 3. The pharmacological characterizations of I_{Tau} with different agonist concentrations. **A** Examples of currents evoked by different concentrations of Tau (Aa, 1 mM; Ab, 3 mM; Ac, 10 mM) and their inhibitions by bicuculline (Bic, 10–30 μM) and strychnine (Str, 1–30 μM) in three different isolated neurons. **B** Pooled inhibitions of 1 mM, 3 mM and 10 mM taurine-evoked currents by Bic and Str in the conditions indicated in the graph. The inhibitions of Bic on I_{Tau} evoked by 1 mM, 3 mM and 10 mM Tau were 0.1 ± 2%, 21 ± 3.2% and 40.3 ± 11.6% respectively; the inhibitions of Str on I_{Tau} evoked by 1 mM, 3 mM and 10 mM Tau were 96.0 ± 2.8%, 84.8 ± 4.0% and 57.5 ± 8.8% respectively. The number of experiments is shown in parentheses.

KA-induced potentiation on I_{Tau}

Our aforementioned studies showed that kainic acid (KA), an agonist of non-NMDA glutamate receptors, facilitated I_{Gly} via Ca^{2+} entry in rat spinal neurons (Xu et al., 1999). Ca^{2+} was a very important factor of many cell-damaging conditions, and here we employed KA to stimulate Ca^{2+} influx and perhaps excitotoxic conditions to examine their modulation on I_{Tau}.

After stable taurine responses were obtained, a solution containing 0.3 mM KA was applied immediately followed by the application of taurine. The amplitude of I_{Tau} was reversibly potentiated by preceding 0.3 mM KA administration in 17 out of 20 neurons tested. In the other three neurons, 0.3 mM KA produced no obvious effects on I_{Tau}. The potentiated lasted several minutes (3–10 min), and then came back to normal (data not shown). A concentration of 0.3 mM KA and an interval of 3–6 s between the applications of the two drugs were selected for all the following experiments. The amplitudes of 1 mM and 10 mM I_{Tau} were increased to 147.2 ± 4.5% (n = 12) and 129.1 ± 9.1% (n = 5) respectively (Fig. 4A,B). In Ca^{2+}-free bath solution, 0.3 mM KA failed to enhance I_{Tau} (100.2 ± 2.2%, n = 6 and 99.5 ± 1.3%, n = 4, for 1 mM and 10 mM taurine response respectively, Fig. 4C). To determine whether the entry of Ca^{2+} exclusively through non-NMDA receptors without voltage dependent Ca^{2+} channels (VDCCs) is sufficient to induce Ca^{2+}-dependent modulation of I_{Tau}, we established experimental conditions that excluded the activation of VDCCs and found that even in the presence of Cd^{2+} (0.2 mM), the blocker of VDCCs, I_{Tau} was enhanced by 0.3 mM KA to the same extent (146.8 ± 3.4%, n = 5 and 130.0 ± 4.3%, n = 4, for 1 mM and 10 mM I_{Tau}, respectively, Fig. 4C) as that in normal conditions. The results indicate that increase of $[Ca^{2+}]_i$ through the activated non-NMDA receptors is sufficient for the effect of KA on I_{Tau} in the present experimental condition.

Discussion

In our study, the antagonist experiment and the cells without glycine response, showed that taurine could activate both glycine and $GABA_A$ receptors in most immature rat hippocampal neurons. This is in full agreement with the *in situ* hybridization studies, which have shown that glycine receptors existed in developing but not adult rat hippocampal CA1 areas (Malosio et al., 1991), while $GABA_A$ receptors existed during most of the lifespan of the rat (Laurie et al., 1992).

Our work also indicated that a concentration of taurine in the range of 0.1–1 mM was likely to activate predominantly strychnine-sensitive glycine receptors. This together with the findings that there were particularly abundant taurine (Huxtable, 1989, 1992; Sturman, 1993) and some glycine receptors (Malosio et al., 1991; Ito and Cherubini, 1991) in immature rat hippocampal CA1, further supported the hypothesis that taurine may act as endogenous agonist at glycine receptors (Mori et al., 2002) as Flint et al. (1998) previously proposed in neocortex. On the other hand, taurine only activated $GABA_A$ receptors with relatively high concentrations.

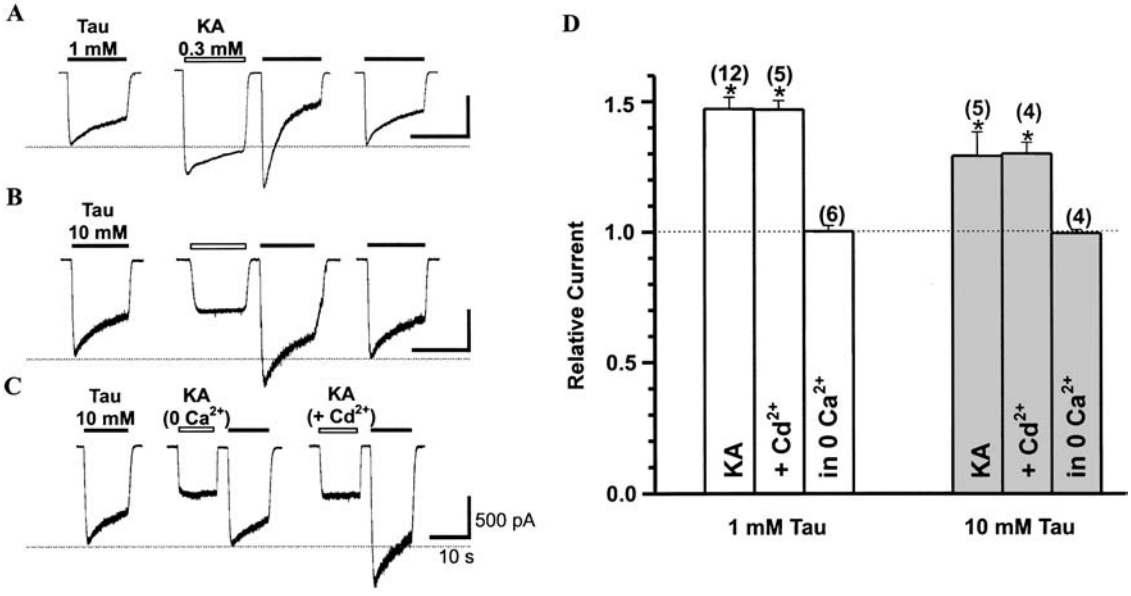

Fig. 4. Ca^{2+} dependence of KA-induced potentiation of I_{Tau}. (A, B) I_{Tau} evoked by 1 mM Tau (**A**) and 10 mM Tau (**B**) were reversibly potentiated by a preceding 0.3 mM KA administration. **C** Ca^{2+}-free bath antagonize the effect of 0.3 mM KA on 10 mM Tau, but 0.2 mM $CdCl_2$ has no antagonistic. **D** Pooled percentage facilitation of 1 mM and 10 mM taurine-evoked currents by 0.3 mM KA in the conditions indicated within the corresponding columns. $*P < 0.05$

However, our work also showed that low-level taurine activated $GABA_A$ receptors when pretreated with 3 μM etomidate (an imidazole general anesthetic, data not shown). This is consistent with previous studies, which showed that etomidate at a clinically relevant concentration of 4.1 μM shifted the GABA dose response to the left with no change in the maximum current evoked by saturating concentrations of GABA in cultured hippocampal neurons (Yang et al., 1996), while glycine-evoked responses mediated by glycine α1 receptors were little influenced by etomidate (Belelli et al., 1999). This indicated that glycine and $GABA_A$ receptors could be modulated diversely, and endogenous taurine can activate $GABA_A$ receptors dominantly when treated with anesthetic that is highly selective for $GABA_A$ receptors.

Although strychnine and bicuculline are well-established antagonists of glycine and $GABA_A$ receptors, respectively, a certain degree of cross-reactivity is apparent. This made it difficult to choose the proper concentration of antagonist that only antagonized one kind of receptors totally and with no effect on another kind of receptors. Moreover, there were non-additive interactions between glycine and $GABA_A$ receptors in rat hippocampal neurons when high concentration of agonist was employed (Li et al., 2002). So, when both receptors were activated, it was hard to estimate their single contributions to the whole taurine response accurately.

Previous work showed that the EC_{50} (dose that produces half-maximal response) of glycine was around 40 μM in the acutely dissociated immature rat hippocampus (Ren et al., 1999; Ye et al., 1999), and the EC_{50} of GABA was around 9 and 33 μM in different rat cultured hippocampal neurons (Schonrock and Bormann, 1993; Aguayo et al., 1994; Birnir et al., 2001). While the EC_{50} of taurine to the glycine receptors was around 128 μM in the rat sacral dorsal commissural neurons (Wang et al., 1998). In the present study, the EC_{50} of taurine to $GABA_A$ receptors was definitely in the mM range. It is proposed that taurine possessed some unique physicochemical properties as it differs from glycine and GABA in being a sulfonic rather than a carboxylic amino acid. Maybe it is the sulphonate group that reduces the binding affinity of taurine to both receptors. Furthermore, there is low-affinity binding site for taurine on the neutral phospholipids of the membrane, with an affinity within the intracellular range of taurine concentrations (Huxtable, 1992, 2000). Thus, taurine may not only act as a receptor agonist, but also act as a modulator of the plasma lipid environment. The aforementioned actions interact

with each other and may make the actions of taurine more complex.

We employed 0.3 mM KA to stimulate Ca^{2+} influx and perhaps excitotoxic conditions. The results showed that pretreated with KA could up-regulate taurine responses and the potentiations were Ca^{2+}-dependent. Most previous studies showed that the modulations of $[Ca^{2+}]_i$ on glycine and $GABA_A$ receptors were mainly due to the phosphorylation states of these receptors and some related proteins which were regulated by coactivation of Ca^{2+}/calmodulin-dependent protein kinase II and calcineurin (Xu et al., 1999; Xu et al., 2000; Kano et al., 2001). However Fucile et al. (2000) suggested that phosphorylation and G-protein pathways appeared not to be involved in the potentiation mechanism of glycine receptors, and that some other diffusible cytoplasmic factor might modulate the effect. So there is still some work needed to illustrate the mechanism of the potentiation.

The enhancement of taurine and glutamate release under cell damage conditions (Saransaari et al., 2000b), and the spatio-temporal relationship of their distribution during development and regeneration (Magnusson, 1996), both suggested that taurine might be the important modulator preventing excitotoxicity. Our observation that the potentiation of I_{Tau} caused by KA and NaCN (data not shown) suggested that the enhancement of neural inhibition under cell damage conditions was not only due to the release of taurine but also due to the altered functions of related receptors.

Most of all, the functions of taurine shouldn't be invariable as previous works showed that the Cl^- equilibrium potential and the receptors changed dramatically during development in the rat hippocampus. Taurine responses are excitatory during the first postnatal week and then become inhibitory (Ito and Cherubini, 1991), while taurine activates glycine and $GABA_A$ receptors during the first two to three postnatal weeks and then only activates $GABA_A$ receptors (Malosio et al., 1991; Laurie et al., 1992).

In conclusion, in the immature rat hippocampus endogenous taurine predominantly activates strychnine-sensitive glycine receptors except for some special conditions, and taurine may antagonize excitotoxicity by enhancing neural inhibition through the activations of glycine and/or $GABA_A$ receptors.

Acknowledgements

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