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ORIGINAL ARTICLE

Antinociceptive effect of intrathecal administration of hypotaurine in rat models of inflammatory and neuropathic pain

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Abstract Hypotaurine is an intermediate in taurine biosynthesis from cysteine in astrocytes. Although hypotaurine functions as an antioxidant and organic osmolyte, its physiological role in the central nervous system remains unclear. This study used behavioral assessments to determine whether hypotaurine influenced nociceptive transmission in acute, inflammatory, and neuropathic pain. The tail flick, paw pressure, and formalin tests were performed in male Sprague–Dawley rats to examine the effects of the intrathecal administration of hypotaurine (100, 200, 400, 600 μg) on thermal, mechanical, and chemical nociception. Chronic constriction injury (CCI) to the sciatic nerve was induced in the rats, and the electronic von Frey test and plantar test were performed to assess the effects on neuropathic pain. To determine which neurotransmitter pathway(s) was involved in the action of hypotaurine, in this study, we examined how the antagonists of spinal pain processing receptors altered the effect of 600 μg hypotaurine. To explore whether hypotaurine affected motor performance, the Rotarod test was conducted. Hypotaurine had antinociceptive effects on thermal, mechanical, and chemical nociception in the spinal cord. In CCI rats, hypotaurine alleviated mechanical allodynia and thermal hyperalgesia. These effects were reversed completely by pretreatment with an intrathecal injection of strychnine, a glycine receptor antagonist. Conversely, hypotaurine did not affect motor performance. This study demonstrated that intrathecal hypotaurine suppressed acute, inflammatory, and neuropathic pain. Hypotaurine may regulate nociceptive transmission physiologically by activating glycinergic neurons in the spinal cord, and it is a promising candidate for treating various pain states.

Keywords Glycinergic neurotransmission · Spinal cord · Taurine · Nociceptive transmission

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Introduction

Hypotaurine (2-aminoethanesulfinic acid) is an intermediate in taurine biosynthesis from cysteine in astrocytes (Banerjee et al. 2008). Taurine is one of the most abundant free amino acids, and it has a number of physiological and pharmacological actions in the central nervous system (CNS) (Albrecht and Schousboe 2005; Gupta 2006). Unlike taurine, the role of hypotaurine in the CNS remains to be fully determined. A large body of evidence indicates that hypotaurine acts as a strong antioxidant (Aruoma et al. 1998; Mehta and Dawson 2001; Bousquet et al. 2010). A previous report showed that hypotaurine suppressed the spike discharges of Purkinje cells in the guinea pig cerebellum (Okamoto and Sakai 1981). The inhibitory effect was blocked by picrotoxin, a γ-aminobutyric acid type A ($GABA_A$) receptor antagonist, and strychnine, a glycine receptor antagonist, suggesting that hypotaurine may be involved in inhibitory neurotransmission. However, no reported study has examined the effects of hypotaurine on nociceptive transmission. The dorsal horn of the spinal cord is an important site in nociceptive transmission, and glycinergic and GABAergic neurons there have recently been implicated as having a crucial role in the inhibition of spinal pain processing in peripheral inflammation and chronic pain (Zeilhofer 2005; Enna and McCarson 2006;

Zeilhofer and Zeilhofer 2008). In this study, we determined whether spinally injected hypotaurine, a precursor of taurine, was effective in alleviating acute, inflammatory, and neuropathic pain.

In this study, we used behavioral assessments to examine the antinociceptive effect of hypotaurine in rats. To understand the effects on acute and persistent pain, the tail flick, paw pressure, and formalin tests were performed. For neuropathic pain, chronic constriction injury (CCI) of the sciatic nerve was induced, and the electronic von Frey test and plantar test were performed. To understand which neurotransmitter pathway(s) is involved in the action of hypotaurine, this study examined how some antagonists of the receptors involved in spinal pain processing influence the effect of hypotaurine. Because the inhibitory interneurons in the spinal cord affect motor function, the Rotarod test was conducted to assess motor performance.

Materials and methods

Animals and drug preparation

The present study was approved by the Ethics Committee of Animal Care and Experimentation at the University of Occupational and Environmental Health, Japan. 200 male Sprague–Dawley rats (Kyudo, Fukuoka, Japan) weighing 180–250 g were used in this study. Rats were housed with free access to food and water, and were maintained on a 12 h light–dark cycle at a constant room temperature of 22 ± 2°C and humidity of 50 ± 5%. All experiments were performed at the same time (between 10:00 and 16:00) during the light period. Rats were assigned randomly to treatment groups, with the experimenter blind to the drug treatments. All experimental groups consisted of six or eight rats. After the experiments, the rats were killed with intraperitoneal injection of urethane.

Hypotaurine, pentobarbital sodium, strychnine hydrochloride, (+)-bicuculline, naloxone hydrochloride, urethane, and dimethyl sulfoxide (DMSO) were purchased from Sigma (St. Louis, MO, USA). Polyethylene catheters (PE-10) were obtained from Becton, Dickinson and Company (San Jose, CA, USA). Bicuculline was dissolved in 100% DMSO. The other drugs were dissolved in 0.9% physiological saline.

Intrathecal catheter implantation

For the intrathecal administration of drugs, lumbar catheters were implanted in all rats according to the procedure outlined by Yaksh and Rudy (1976). Under anesthesia using pentobarbital sodium (60 mg/kg, intraperitoneal), a stretched PE-10 polyethylene catheter (8.5 cm) was inserted into the intrathecal space and advanced caudally to the rostral edge of the lumbar enlargement through an incision in the atlanto-occipital membrane. A recovery period of seven days was provided before intrathecal administration of hypotaurine and behavioral assessment. Proper location of the catheter was confirmed by hind limb paralysis after the injection of 10 μL of 2% lidocaine 2 days before the assessment. For assays, 10 μL of the drugs or saline was administered intrathecally, followed by 10 μL of saline to flush the catheter.

Tail flick test

A radiant heat source was focused on the middle part of the rat's tail. The time interval from the onset of the stimulus until the tail flick response was measured using a tail flick unit (7360; Ugo Basile, Comerio, Italy). The intensity of the radiant heat was adjusted to give a tail flick latency of 4–5 s before the administration of hypotaurine or saline. In the absence of a response, the stimulus was terminated after 15 s (cutoff) to prevent tissue damage. The effects of hypotaurine (100, 200, 400, and 600 μg) on thermal nociception were assessed repeatedly for 120 min post-injection. The measured reaction latencies (s) were converted to the percentage of the maximum possible effect (%MPE) according to the formula: %MPE = [(hypotaurine-treated latency) − (saline-treated latency)]/[15 − (saline-treated latency)] × 100.

Paw pressure test

To test the effect of hypotaurine on mechanical nociception, the vocalization threshold of paw pressure was measured as described by Randall and Selitto (1957) using an analgesy-meter (model 37215; Ugo Basile, Comerio, Italy) in normal rats. Increasing pressure (32 g/s) was applied through a plastic tip onto the dorsal surface between the third and fourth metatarsus of the left hind paw until the rat squeaked. Vocalization threshold was expressed in grams, and the cutoff was 500 g. Threshold measurements were repeated twice and the average was taken. The effects of hypotaurine (200, 400, and 600 μg) and saline were assessed repeatedly for 90 min post-injection. The measured thresholds (g) were converted to the percentage of the maximum possible effect (%MPE) according to the formula: %MPE = [(hypotaurine-treated threshold) − (saline-treated threshold)]/[500 − (saline-treated threshold)] × 100.

Formalin test

Rats were first placed in a plastic observation chamber (25 × 25 × 30 cm) for at least 15 min to acclimate to the environment. The rats were subcutaneously injected into

the plantar surface of the hind paw with 50 μL of 5% formalin solution using a 27-gauge needle. The formalin injection produced the characteristic pain response: biphasic flinching/shaking of the injected paw. Such pain behaviors were quantified by periodically counting the number of spontaneous flinching/shaking. They were counted for 1-min periods at 1–2 min, 5–6 min, and then for 1-min periods at 10-min intervals from 10 to 60 min after the formalin injection. Because the observed pain behavior was biphasic, the evaluation of the flinching/shaking response was divided into two phases, Phase I (0–10 min) and Phase II (10–60 min), after formalin injection. To investigate the effect of hypotaurine (200, 400, and 600 μg) and saline was administered intrathecally 15 min before formalin injection.

CCI model

On the same day as the intrathecal catheter implantation, peripheral neuropathy was induced using a slight modification of the procedure described by Bennett and Xie (1988). Briefly, the left sciatic nerve was exposed at mid-thigh level. Proximal to the sciatic trifurcation, four loose 4–0 silk ligatures were tied around the nerve at 1-mm intervals. To confirm an influence of nerve injury, a sham operation was performed with exposure of the left sciatic nerve without the application of ligatures. Baseline levels of CCI rats in behavioral tests were compared with those of the sham-operated rats.

Electronic von Frey test

Mechanical allodynia was assessed by measuring the withdrawal threshold of the left hind paw in response to a mechanical stimulus using an electronic von Frey aesthesiometer (model 2391C; IITC Life Science, Woodland Hills, CA, USA). Each animal was placed on a metallic grid floor in a plastic observation chamber, which provided access to the plantar surface of the hind paw. Animals were allowed to acclimate to the environment for 15 min. A rigid tip attached to the meter was applied to the left plantar surface from under the floor. The withdrawal threshold was defined as the average force (g) required to withdraw the stimulated paw in five trials separated by a 1-min interval to prevent mechanical sensitization and tissue damage. The effects of hypotaurine (200, 400, and 600 μg) and saline were assessed repeatedly in CCI rats for 90 min post-injection.

Plantar test

Thermal hyperalgesia was assessed by measuring hind paw withdrawal latency in response to radiant heat using a plantar test apparatus (model 7360; Ugo Basile) according to the method outlined by Hargreaves et al. (1988). Each rat was placed into compartment enclosures on a glass surface. A mobile heat source was then positioned under the plantar surface of the hind paw and activated with a light beam, giving withdrawal latencies from 8 to 10 s in normal rats. The digital timer automatically recorded the response latency for paw withdrawal to the nearest 0.1 s. A cutoff time of 20 s was imposed to prevent tissue damage in the absence of a response. The mean withdrawal latencies for the left hind paw were determined from the average of two trials separated by a 5-min interval to prevent thermal sensitization. The effects of hypotaurine (200, 400, and 600 μg) and saline were recorded repeatedly in CCI rats for 90 min post-injection. The measured reaction latencies (s) were converted to the maximum possible effect (%MPE) according to the following formula: $\%\text{MPE} = [(\text{hypotaurine-treated latency}) - (\text{saline-treated latency})]/[20 - (\text{saline-treated latency})] \times 100$.

Rotarod test

The influence on motor performance was assessed using an accelerating rotarod (model 47700; Ugo Basile) as described previously (Haranishi et al. 2010), in which normal rats were placed on a rotating drum with the speed increasing from 4 to 40 rpm over 5 min. The rats were forced to make forward-walking movements to avoid falling. The latencies (s) to fall were measured. Training sessions were carried out 1 and 2 days prior to the experiments, with three trials on each day. On the experimental day, a baseline response was obtained and the rats were subsequently administered hypotaurine (200, 400, or 600 μg) or saline.

Involvement of endogenous pain modulatory systems

To examine whether the action of hypotaurine is mediated by a glycinergic, GABAergic, or opioid system, the following receptor antagonists were administered intrathecally prior to 600 μg hypotaurine: strychnine (5 μg), a glycine receptor antagonist; bicuculline (10 μg), a $GABA_A$ receptor antagonist; and naloxone (10 μg), a μ-opioid receptor antagonist. The effects of these antagonists on the antinociception induced by hypotaurine were evaluated for mechanical nociceptive threshold in normal rats, and for thermal hyperalgesia in CCI rats at 15 min post-injection.

Statistical analysis

Data are represented as the mean ± standard deviation. To compare the antinociceptive effects of three doses of hypotaurine with saline in tail flick test, paw pressure test and plantar test, the differences were determined by non-parametric Mann–Whitney U test. The differences between

hypotaurine and saline in formalin test, electronic von Frey test, and rotarod test and the differences between 600 μg hypotaurine and three receptor antagonists in paw pressure test and plantar test were determined by one-way analysis of variance followed by Dunnett's test. The differences in baseline levels between CCI and sham-operated rats in electronic von Frey test and plantar test were determined by Student's two-sample t test. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Differences were considered significant at two-sided $P < 0.01$.

Results

Antinociceptive effects on thermal, mechanical and chemical nociception

To determine whether hypotaurine modulates thermal nociception, the tail flick test was performed. Hypotaurine prolonged the tail flick latencies in a dose-dependent manner (Fig. 1a). Significant effects were observed at 200 μg hypotaurine and higher doses. To examine the effect of hypotaurine on mechanical nociception were subjected to the Randall–Selitto test. Baseline level of vocalization threshold before intrathecal injection was 230 ± 38 g. Hypotaurine dose-dependently increased the vocalization threshold compared to saline (Fig. 1b). Significant increases were observed with 200 μg hypotaurine and higher doses (Fig. 1b). To further examine whether hypotaurine causes an antinociceptive effect on chemical stimulation, the formalin test was performed. Hypotaurine suppressed the flinching/shaking behavior in both phases (Fig. 2a). Calculation of the area under curve (AUC) revealed that 400 μg and higher doses of hypotaurine significantly decreased the flinching/shaking behavior in Phase II, whereas only 600 μg hypotaurine inhibited in Phase I (400 μg, $P = 0.022$) (Fig. 2b).

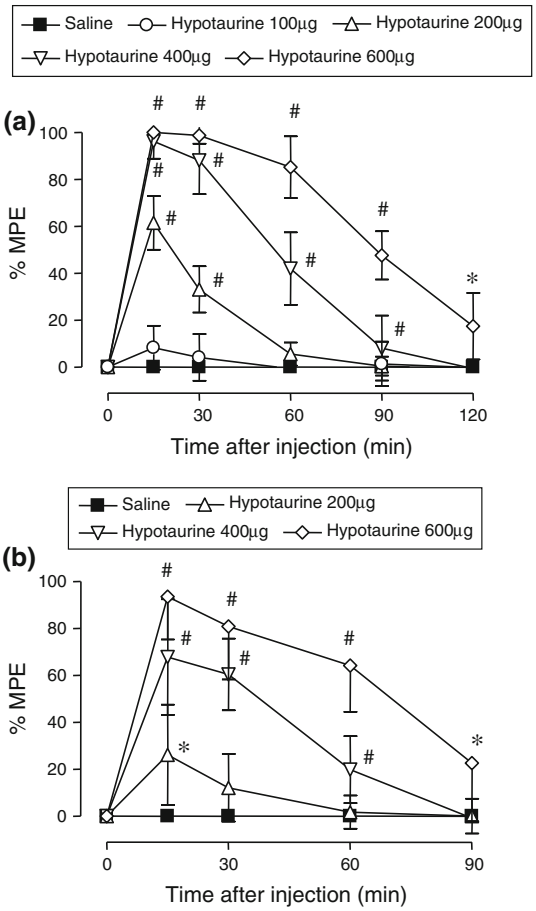

Fig. 1 Effect of intrathecal administration of hypotaurine on thermal and mechanical nociception in normal rats. **a** Tail flick test. Hypotaurine increased the tail flick latency and prolonged the duration of action. Significant effects were seen at 200 μg and higher doses. **b** Randall–Selitto test. Hypotaurine elevated the vocalization threshold and prolonged the duration of action in a dose dependent manner. Significant effects were seen at 200 μg and higher doses. Each group consists of eight rats. Data are expressed as the percentage of the maximum possible effect (%MPE) of mean ± SD. $^{*}P < 0.01$, $^{\#}P < 0.001$ compared to the saline

Effects of hypotaurine on mechanical allodynia and thermal hyperalgesia

CCI rats showed significant decreases in paw withdrawal thresholds in the electronic von Frey test. The left paw withdrawal threshold after surgery was lower (10.9 ± 3.0 g) than that in sham-operated rats (39.9 ± 6.5 g, $P < 0.001$) (Fig. 3a). Hypotaurine dose-dependently increased the threshold and prolonged the duration of action in the CCI rats. Significant increases were observed with 400 μg hypotaurine and higher doses. To determine whether hypotaurine affects thermal hyperalgesia, the plantar test was performed in the CCI rats. Baseline level of the paw withdrawal latency after surgery was significantly shorter (6.0 ± 0.4 s) than that in sham-operated rats (9.4 ± 0.8 s, $P < 0.001$). Compared to saline, hypotaurine prolonged the paw withdrawal latencies and duration of action in a dose-dependent manner (Fig. 3b). Significant effects were observed with 400 μg hypotaurine and higher doses.

Effects of hypotaurine on motor function

The effect of hypotaurine on motor activity in normal rats was determined by the rotarod test. Baseline latency was 116 ± 7 s. Hypotaurine at levels up to 600 μg did not affect the rotarod latency (Fig. 4).

Involvement of glycinergic neurotransmission in hypotaurine action

In normal rats, the alleviating effect of 600 μg hypotaurine on mechanical nociceptive threshold (93% ± 13%) was

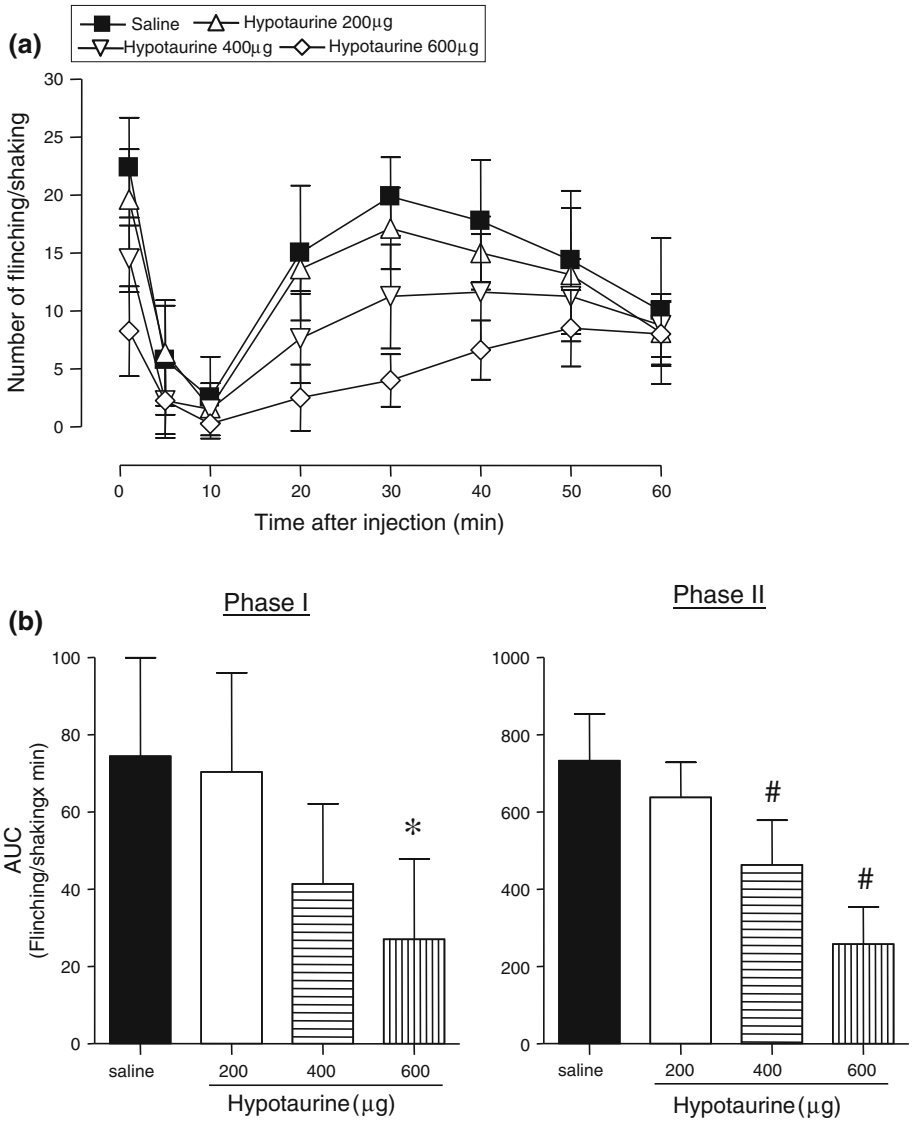

Fig. 2 Antinociceptive effect of intrathecal administration of hypotaurine on formalin-induced paw flinching/shaking behavior. An injection of formalin into the hind paw of rats produced a biphasic pain response. Hypotaurine or saline was applied 15 min before formalin injection. Flinching/shaking was counted for 1-min periods at 1–2 min, 5–6 min, and then for 1-min periods at 10-min intervals from 10 to 60 min after the formalin injection. Data are expressed by the time course curves (**a**) and the area under curve (AUC, number of flinching/shaking × min) (**b**). Each group consists of eight rats. $^{*}P < 0.01$, $^{\#}P < 0.001$ compared to the saline

reversed by pretreatment with strychnine and the vocalization threshold returned to the level of saline (1% ± 8%, $P < 0.001$) (Fig. 5a). Similarly, in CCI rats, the alleviating effect of 600 μg hypotaurine on thermal hyperalgesia (87% ± 14%) was reversed by pretreatment with strychnine and the withdrawal latencies returned to the level of saline (6% ± 11%, $P < 0.001$) (Fig. 5b). However, neither bicuculline nor naloxone affected the effect of hypotaurine on the mechanical nociception or thermal hyperalgesia.

Discussion

The physiological role of hypotaurine in the CNS is not fully understood. Several studies have shown that hypotaurine is a strong antioxidant (Aruoma et al. 1998; Mehta and Dawson 2001; Bousquet et al. 2010). It may be important as an organic osmolyte for proper CNS function, like taurine (Zwingmann and Leibfritz 2005). This study showed, for the first time, the antinociceptive effects of intrathecally administered hypotaurine on acute, persistent, and neuropathic pain. Hypotaurine elevated the thermal and mechanical nociceptive threshold in the tail flick and paw pressure tests. The tail flick response is recognized as a spinally integrated nociceptive reflex, whereas vocalization is a more integrated pain response that involves a supraspinal mechanism on acute nociceptive processing. The formalin test is used widely for assessing chemically induced acute and persistent pain (Tjolsen et al. 1992). A biphasic response is observed after the intraplantar injection of formalin in the hind paw of rats. The early phase is the response to direct chemical stimulation of nociceptors via Aδ and C-fibers, and the late phase is attributed to peripheral inflammatory processes and subsequent sensitization of nociceptive spinal neurons (Coderre et al. 1993). Our results indicate that hypotaurine suppresses

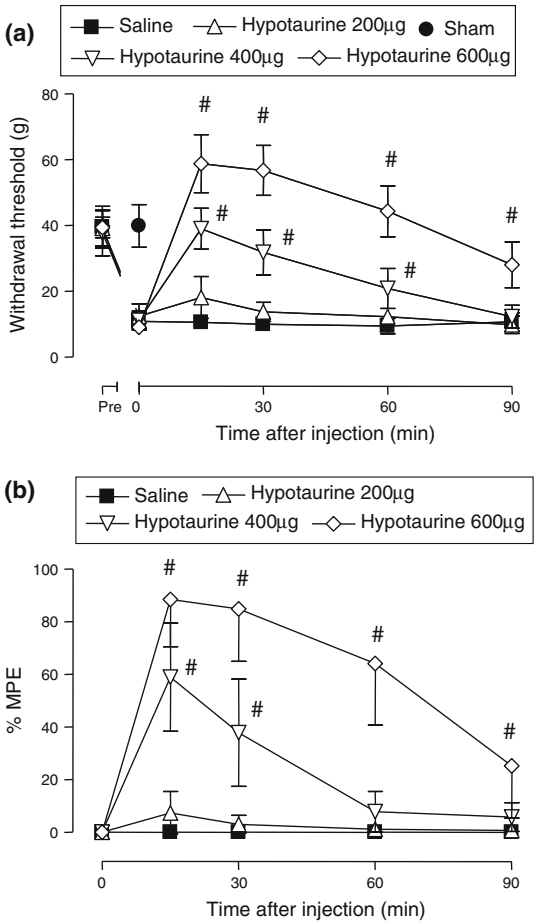

Fig. 3 Effect of intrathecally administered hypotaurine on mechanical allodynia and thermal hyperalgesia in chronic constriction injury (CCI) models. **a** Electronic von Frey test. In CCI rats, left paw withdrawal threshold after surgery was significantly lower than that in sham-operated rats. Hypotaurine increased the paw withdrawal threshold and prolonged the duration of action. Significant effects were seen at 400 μg and higher doses. Data are expressed as the threshold in grams of mean ± SD. **b** Plantar test. Hypotaurine increased the paw withdrawal latency and prolonged the duration of action. Significant effects were seen at 400 μg and higher doses. Data are expressed as the percentage of the maximum possible effect (%MPE) of mean ± SD. Each group consisted of eight rats. $^{*}P < 0.01$, $^{\#}P < 0.001$ compared to the saline

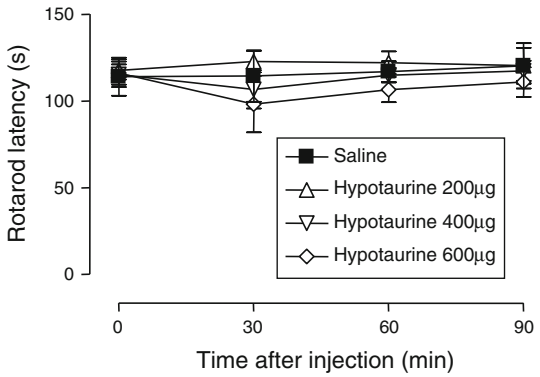

Fig. 4 Effect of intrathecally administered hypotaurine on motor performance in the rotarod test using normal rats. Hypotaurine did not affect motor performance at levels up to 600 μg. Data are expressed as latencies of the mean ± SD. Each group consisted of six rats

nociception via direct chemical stimulation in Phase I, and inhibits the nociceptive response to persistent pain in Phase II. Hypotaurine reduced both spinally and supraspinally integrated pain responses.

Chronic constriction injury to the sciatic nerve resulted in mechanical allodynia and thermal hyperalgesia, demonstrated by the electronic von Frey and plantar tests. Light touch applied in von Frey test is mediated via Aβ afferent fibers while mechanical nociception produced by paw pressure activates Aδ and C-fibers. Hypotaurine dose-dependently inhibited mechanical allodynia and thermal hyperalgesia in the CCI model. To determine the mechanism by which hypotaurine exerts its analgesic action, antagonists to the receptors involved in spinal pain processing were examined. Recently, the glycinergic and GABAergic neurons in the dorsal horn of the spinal cord have emerged as pivotal inhibitory modulators of spinal pain processing in inflammatory and neuropathic pain (Zeilhofer 2005; Enna and McCarson 2006; Zeilhofer and Zeilhofer 2008). An increase in the mechanical nociceptive threshold in normal rats and alleviation of thermal hyperalgesia in the CCI rats by high dose of hypotaurine were reversed completely by strychnine, a glycine receptor antagonist, whereas neither bicuculline nor naloxone affected the mechanical or thermal thresholds. This result is partly supported by an in vitro study in which strychnine and picrotoxin blocked the inhibitory actions of hypotaurine in cerebellum slices (Okamoto and Sakai 1981). Our experiments could not demonstrate the involvement of the GABA system in the action of hypotaurine, however, our results do not necessarily mean that $GABA_A$ and opioid receptors are not associated with the hypotaurine's effect. The discrepancy with the present study is probably derived from differences of assay conditions, routes of drug administration and behavioral tests. In the spinal cord, inhibitory neurotransmission is predominantly mediated by glycinergic neurons rather than GABAergic neurons or opioid system. Provided the action of hypotaurine is derived only from $GABA_A$ or opioid receptors, the action should be antagonized by bicuculline or naloxone. Therefore, it would appear that with regard to the action of high dose hypotaurine, $GABA_A$ or opioid receptors are much less involved in the hypotaurine action than glycine receptors. However, submaximal antinociceptive effect by low dose hypotaurine may be affected partially by naloxone or bicuculline. Our results suggest that the maximal antinociceptive effect of hypotaurine is, in significant part, derived from the activation of glycinergic neurons. Previously, we demonstrated that the activation of glycinergic

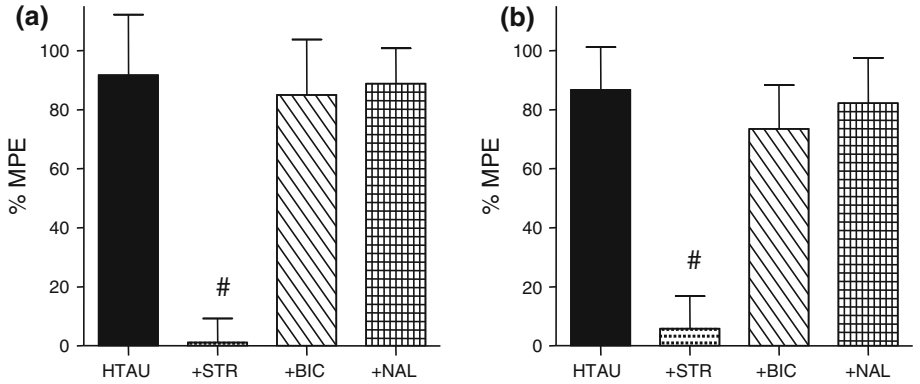

Fig. 5 Involvement of endogenous pain modulatory systems in hypotaurine action. Alleviating effects of 600 μg hypotaurine (HTAU) on mechanical nociception in normal rats (**a**) and thermal hyperalgesia in chronic constriction injury rats (**b**) at 15 min post-injection were reversed by pretreatment with strychnine (STR). On the other hand, neither bicuculline (BIC) nor naloxone (NAL) significantly affected the hypotaurine action. Data are expressed as the percentage of the maximum possible effect (%MPE) of mean ± SD. Each group consisted of six rats. $^{\#}P < 0.001$ compared to hypotaurine (600 μg)

neurotransmission by a glycine reuptake inhibitor exerted remarkable antinociception in a rat acute pain model (Haranishi et al. 2010). Glycine injected intrathecally alleviated mechanical hyperalgesia in a rat neuropathic pain model (Huang and Simpson 2000). Our results, combined with previous investigations, indicate that the glycinergic system is a pivotal component modulating nociceptive transmission in the spinal cord.

Taurine, an oxidative metabolite of hypotaurine, has been proven to be antinociceptive in animal models of acute, inflammatory and neuropathic pain (Smullin et al. 1990; Silva et al. 1993; Serrano et al. 1994; Belfer et al. 1998; Pellicer et al. 2007). Our recent study showed that intrathecally administered taurine has pain-relieving effects via activating glycine receptors in different models of neuropathic pain (Terada et al. 2011). Evidence obtained from previous research indicates that conversion of hypotaurine to taurine occurs in astrocytes. Putative pathway of taurine synthesis from administered hypotaurine and taurine efflux in astrocyte is shown in Fig. 6. Hypotaurine and taurine are actively transported into astrocytes and neurons by sodium-dependent taurine transporters. Essential enzymes that convert cysteine to taurine, including cysteine dioxygenase, cysteine sulfinic acid decarboxylase, and hypotaurine dehydrogenase, have been found only in astrocyte, but not elsewhere. Oxidation of hypotaurine to taurine is catalyzed by putative hypotaurine dehydrogenase. Brand et al. (1998) showed that hypotaurine and taurine were synthesized in vitro from cysteine by astrocytes and that conversion of hypotaurine to taurine lasted for >72 h after incubation, indicating that the conversion proceeds at a slow rate. Furthermore, a recent study (Vitvitsky et al. 2011) demonstrated that incubation of astrocytes with cysteine led to accumulation of intracellular hypotaurine, however, a corresponding increase in taurine

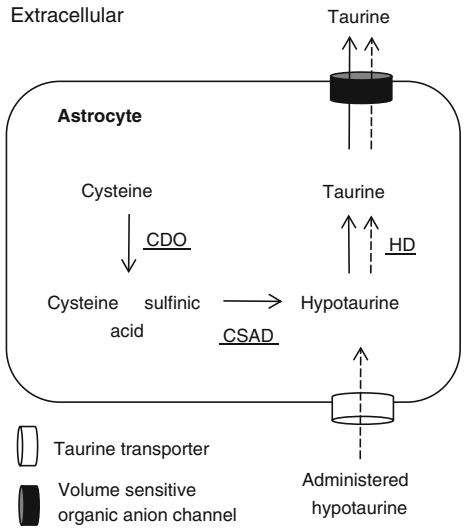

Fig. 6 Scheme representing putative pathway from hypotaurine uptake to taurine efflux in astrocyte. *Solid arrows* depict biosynthesis of taurine from cysteine and efflux in response to change in osmotic condition. *Dashed arrows* depict conversion of spinally injected hypotaurine to taurine and subsequent efflux. *CDO* cysteine dioxygenase, *CSAD* cysteine sulfinic acid decarboxylase, *HD* hypotaurine dehydrogenase

concentration was not observed, suggesting that conversion of hypotaurine to taurine is tightly regulated. Considering that antinociceptive action of hypotaurine appeared within 15 min post-injection, the action observed in the present study is thought to be mediated mostly by hypotaurine per se, but not taurine. Although the localization of hypotaurine in the spinal cord has not been determined in humans, it is reasonable to think that hypotaurine coexists with taurine in spinal nociceptive neurons. Thus, our results suggest that endogenous hypotaurine may serve as a physiological regulator of nociceptive transmission in the spinal cord.

We also demonstrated that hypotaurine did not affect motor performance at levels up to 600 μg, at which a marked antinociceptive effect was seen. This property of hypotaurine may be advantageous clinically. Our recent study showed that spinally applied taurine at level of 400 μg suppressed motor function (Terada et al. 2011). There is abundant evidence of the existence of functional glycinergic synapses in the motor reflex pathway (Legendre 2001; Lynch 2004). An increase in glycinergic neurotransmission decreases the excitability of motor neurons. It also is known that GABA interneurons pre- and postsynaptically suppress motor neuron in the spinal cord (Betley et al. 2009). Difference of affinity for not only glycine receptor but also spinal $GABA_A$ receptor subtype and/or $GABA_B$ receptor between hypotaurine and taurine may be involved in that of influence on motor function. Because hypotaurine is an endogenous, neuroprotective molecule, it is conceivable that hypotaurine could be a therapeutic agent without serious adverse effects. Further research is required to determine its clinical application.

In conclusion, this study demonstrated that spinally injected hypotaurine had analgesic actions on acute, persistent, and neuropathic pain without influencing motor function. These findings suggest that hypotaurine may be a promising remedy for various pain states.

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Conflict of interest None.

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