Strychnine-dependent in the
urethane-anesthetized rat is segmentally
distributed and prevented by intrathecal
glycine and betaine

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Abstract: The blockade of spinal glycine receptors with intrathecal strychnine produces a reversible allodynia-like state in the rat. Thus, hair deflection, in the presence of intrathecal strychnine, induces cardiovascular and motor withdrawal responses comparable with those evoked by noxious thermal, mechanical, or chemical stimulation in the absence of strychnine. In the present study, we mapped the cutaneous sites of abnormal sensitivity to hair deflection throughout the strychnine time course to investigate the segmental distribution of strychnine-induced allodynia. The ability of intrathecal glycine and the glycine derivative betaine to reverse strychnine-induced allodynia was also determined using dose-response analysis. Following intrathecal strychnine (40 μg), stroking the legs, flanks, lower back, and tail with a cotton-tipped applicator evoked a pronounced increase in mean arterial pressure, tachycardia, and an abrupt motor withdrawal response in urethane-anesthetized rats. These abnormal responses were only evoked by hair deflection at discrete sites, corresponding to the cutaneous dermatomes innervated by spinal segments near the site of strychnine injection. In rats with intrathecal catheters lying laterally in the subarachnoid space, allodynic sites were observed unilaterally on the ipsilateral side of intrathecal strychnine injection. Recovery from strychnine was complete by 30 min in all affected dermatomes. The cardiovascular and motor withdrawal responses to hair deflection were dose-dependently inhibited by intrathecal glycine and intrathecal betaine. The ED$_{50}$ (95% confidence interval) for intrathecal glycine was 609 (429–865) μg for the heart rate response, 694 (548–878) μg for the pressor response, and 549 (458–658) μg for the motor withdrawal response. The corresponding values for intrathecal betaine were 981 (509–1889), 1045 (740–1476), and 1083 (843–1391) μg, respectively. There was no difference in the effect of betaine on sensory-evoked cardiovascular and motor responses. Cortical electroencephalographic activity was not affected by intrathecal glycine or betaine, consistent with a spinal locus of action in reversing strychnine-induced allodynia. These results support the hypothesis that removal of spinal glycnergic modulation from low threshold afferent input with intrathecal strychnine results in segmentally localized, tactile-evoked allodynia.

Key words: intrathecal, glycine, allodynia, strychnine, rat.

Résumé : Le blocage des récepteurs spinaux de la glycine par l'administration de strychnine intrathécale entraîne un état de type allodynie réversible chez le rat. Ainsi, en présence de strychnine intrathécale, le toucher du poil provoque des réponses motrices de retrait et cardiovasculaires comparables à celles induites par une stimulation chimique, mécanique ou thermique nociceptive en l'absence de strychnine. Dans la présente étude, nous avons dressé une carte des sites cutanés présentant une sensibilité anormale à la stimulation pilosensible durant l'injection de la strychnine, afin d'examiner la distribution segmentaire de l'allodynie induite par cette substance. Nous avons aussi effectué une analyse dose-réponse de la capacité de la glycine intrathécale et de son dérivé, bétaïne, de renverser l'allodynie induite par la strychnine. Après l'administration de strychnine intrathécale (40 μg), le fait de toucher légèrement les jambes, les flancs, le bas du dos et la queue avec un porte-coton a provoqué une augmentation marquée de la pression artérielle moyenne, une tachycardie et une réponse motrice de retrait subite chez des...
Introduction

The acute blockade of spinal glycine receptors with intrathecal (i.t.) strychnine (STR) produces a reversible allodynia-like state in the rat. Thus, when conscious rats were treated with i.t. STR, light tactile stimuli provoked vocalization, aggression, and other nociceptive behaviours that are usually elicited only by a noxious stimulus (Beyer et al. 1985, 1988; Sosnowski and Yaksh 1989; Yaksh 1989). In urethane-anesthetized rats given i.t. STR, hair deflection (HD) induced cardiovascular and motor withdrawal responses comparable with those evoked by noxious thermal, mechanical, or chemical stimulation in the absence of STR (Sherman and Loomis 1994, 1995). Importantly, the peripheral substrates and spinal mechanisms underlying these abnormal, STR-dependent responses are distinct from those mediating conventional noiception (Sosnowski and Yaksh 1989; Yaksh 1989; Sherman and Loomis 1994, 1995), and consistent with the definition of allodynia.

The sites of cutaneous sensitivity to HD change with time after i.t. STR. Although detailed studies have not been conducted, these appear to be related to the distribution of STR in the spinal subarachnoid space. For example, at early time points after i.t. STR, the cutaneous areas most sensitive to HD appeared to be those innervated by spinal sites near the STR injection site. At later time points, the area of cutaneous sensitivity expanded, then dissipated, as the effects of STR declined. In the present study, we constructed detailed maps of cutaneous sensitivity throughout the STR time course to investigate the segmental distribution of STR-induced allodynia.

The somatosensory change induced by i.t. STR is believed to arise from the blockade of glycine receptors that modulate the evoked responses of spinal neurons to non-noxious sensory stimulation (e.g., large diameter, myelinated fiber input). However, STR is known to influence biological systems by mechanisms other than glycine receptor antagonism (Barron and Guth 1987; Bertolino and Vicini 1988). Examples of these include direct effects on chloride ion channels (Prichard 1971; Barron and Guth 1987) and antagonism of the actions of γ-aminobutyric acid, noradrenaline, and dopamine (Curtis et al. 1971). Although these nonspecific effects are only observed at STR concentrations several orders of magnitude greater than those required for glycine antagonism (Becker and Betz 1987), it is possible that the injection of a concentrated STR solution into the spinal subarachnoid space of the rat could yield cerebrospinal fluid and tissue concentrations that produce such effects. Therefore, the ability of i.t. glycine and the glycine derivative betaine to reverse STR-induced allodynia was determined using dose-response analysis. Our initial interest in betaine was based on its reported ability to prevent the convulsive action of i.t. STR without affecting the concurrent somatosensory disturbance (Beyer et al. 1988). The ability to discriminate between the sensory and convulsive actions of STR is intriguing, since both are believed to arise from STR blockade of inhibitory glycine receptors (Freed 1985; Beyer et al. 1985, 1988; Yaksh 1989).

Methods

Animals

All experiments were conducted using male, Sprague-Dawley rats (330–450 g at the time of experiment), obtained from Charles River (St-Constant, Que.). Animals were housed in the Animal Care Facility, with a room temperature of 22°C, a 12 h light : 12 h dark cycle (lights on at 07:00), and free access to rat chow and tap water. All experiments were conducted in accordance with the guidelines of the Canadian Council on Animal Care and were approved by the Memorial University Animal Care Committee.

Implantation of i.t. catheters

Under halothane anesthesia, rats were fitted with i.t. catheters prepared from stretched polyethylene tubing (PE-10 pulled to = 1.5 × the original length). As previously described (Sherman and Loomis 1994), the catheters were filled with sterile saline, inserted through the cisterna magna into the
spinal subarachnoid space, and guided 8.5 cm caudally (L1 termination). A fixed loop in the rostral end of the catheter was sutured to the overlying muscle and the incision was closed. The rostral tip was exteriorized and sealed with a stainless-steel plug. Animals were permitted to recover for at least 3 days following the surgery, and only those animals without signs of neurological impairment were used for experimentation.

**Drug administration**

All drugs were dissolved in 0.9% sterile saline (Astra Pharma Inc., Mississauga, Ont.), injected with a hand-held Hamilton microlitre syringe, and flushed through the i.t. catheter with 8–10 μL of sterile saline. Strychnine sulfate (Sigma Chemical Co., St. Louis, Mo.) was administered in a volume of 4 μL to reduce rostro-caudal spread in the cerebrospinal fluid. Betaine and glycine (Sigma) were injected in volumes of 5 and 10 μL, respectively.

**Acute anesthetized animal preparation**

On the day of the experiment, surgical anesthesia was induced with halothane, the left jugular vein was cannulated, and thereafter, anesthesia was maintained using i.v. urethane (10% w/v in saline; Sigma). The initial urethane dose (1.1 g/kg) was infused slowly over 5–10 min as the anesthetic effect of halothane declined. Throughout the experiment, anesthesia was supplemented with i.v. urethane as required. The left carotid artery was cannulated for continuous monitoring of blood pressure and heart rate (HR) with a pressure transducer (P23XL and polygraph (model 79E, Grass Instruments Co., Quincy, Mass.). The incision was sutured and the animal was placed in a stereotaxic frame. The incision and contact points with the ear bars were coated with 2% lidocaine gel (Astra) to reduce basal sensory input. Cortical electroencephalographic activity (EEG) was monitored with two subcutaneous needle electrodes (E2, Grass Instruments) placed 2 mm left of midline, one extending rostrally entering the skin near the bregma, the other extending caudally entering the skin about 2 mm caudal to the first. Body temperature was maintained at 37°C with a thermostatically regulated blanket (Harvard Apparatus Co., Millis, Mass.). The animal was permitted to stabilize for 1 h prior to initiation of the acute experiment.

All experiments were conducted using a light plane of anesthesia as determined by EEG monitoring. With urethane, a relationship has been observed between the proportion of time that the EEG is synchronized and the depth of anesthesia (Angel et al. 1976; Lincoln et al. 1980). For our purposes, light anesthesia was defined as the presence of an EEG pattern that fluctuates between synchrony and desynchrony, with synchrony present for not more than 60% of the time. The basis for the 60% cutoff has been described in a previous publication (Sherman and Loomis 1994).

Hair deflection (HD) was used as an innocuous tactile stimulus. By itself, this stimulus produced little or no change in HR or blood pressure and was not associated with any type of motor withdrawal. Following i.t. STR, the same stimulus resulted in elevation of blood pressure and HR, and an abrupt motor withdrawal response when the HD was applied to a cutaneous dermatome innervated by the spinal region affected by STR (see Results). The HD stimulus was applied for a period of 2 min, during which the legs, flanks, lower back, and tail were sequentially stroked with a cotton-tipped applicator. When a dermatome was found where this stimulus evoked a withdrawal response (after i.t. STR), the region was stroked in an oscillating motion. Oscillating stimuli evoke cardiovascular responses more effectively than a stationary stimulus (Yaksh 1989; Sherman and Loomis 1994).

**Experimental protocols**

Anesthetized rats, prepared as described above, were used for one of the following experimental protocols. As a control for experiments using i.t. glycine or i.t. betaine, each rat received i.t. saline followed either 20 or 30 min later by i.t. STR (40 μg). This dose of STR was chosen on the basis of results of an earlier study demonstrating optimal allodynia with minimal convulsive effects (Sherman and Loomis 1994). Approximately 1 h after this i.t. saline – i.t. STR control, each rat received either i.t. glycine (300, 600, or 1000 μg) or i.t. betaine (300, 600, 1000, or 2000 μg). Twenty minutes after each betaine treatment, or 30 min after each glycine treatment, i.t. STR (40 μg) was administered. HD was applied to the legs, flanks, lower back, and tail of the animal 5 min prior to i.t. STR and at 5-min intervals for 30 min after each STR administration. The pretreatment times enabled the drugs to reach their peak effects, based on results of preliminary experiments. The pretreatment time for the saline – STR control was always the same as for the drug being tested in that animal. Most animals received two doses of either i.t. glycine or i.t. betaine. Before administration of a second dose, the i.t. saline – i.t. STR control was repeated; a second dose was administered only if the effects of the initial dose were no longer present, as evidenced by a return of all responses to the level of the first i.t. saline – i.t. STR control. In animals receiving two doses of drug, the first dose selected was always lower than the second to reduce the time required for recovery between doses and to minimize the possibility of a carry-over effect.

To map the time-related changes in the areas of cutaneous sensitivity to HD after i.t. STR, data from i.t. saline – i.t. STR control groups were selected on the basis of the position of the caudal end of the catheter in the spinal subarachnoid space. That is, data were included only if the tip of the i.t. catheter was located at least 2 mm lateral to the midline on either the left or the right side. Side to side as well as rostro-caudal changes in cutaneous sensitivity were compared over time in animals with either left or right i.t. catheters. At the time of autopsy, 27 of the 76 animals whose cutaneous sensitivity had been mapped met this criterion.

**Data analysis**

All blood pressure data are presented as changes in mean arterial pressure (MAP) calculated from the following equation: MAP = systolic blood pressure + 1/3 pulse pressure. Since we were interested in the responses evoked by the HD stimulus, the change in MAP or HR has been reported relative to the immediate prestimulus control (not relative to \( t = 0 \)) for each point in the time course. More precisely, maximum HR or MAP observed in the 1-min interval before stimulus application was subtracted from the maximum value observed during stimulus application, and this difference was reported. Note that only peak responses evoked by HD
Fig. 1. Time course of intrathecal (i.t.) strychnine (STR) dependent motor withdrawal responses evoked by hair deflection (HD) as determined by the area of abnormal cutaneous sensitivity. The percent of anesthetized rats (shading) exhibiting a motor withdrawal response to HD applied within a (rectangular) cutaneous region is shown as a function of time after i.t. STR (40 μg). The rostrocaudal distribution of sensitivity to HD suggests that i.t. STR affects discrete spinal segments rather than eliciting generalized spinal disinhibition. The data presented are from rats with i.t. catheter tips located either to (A) the left (n = 9) or (B) the right (n = 18) of midline at the lumbar enlargement (>2 mm from the midline). Note that a greater percentage of animals exhibit sensitivity to HD in cutaneous regions ipsilateral to the i.t. catheter tip (which presumably corresponds to the site of STR delivery at t = 0).

A. Intrathecal Catheter Position: Left of Midline

B. Intrathecal Catheter Position: Right of Midline

Time: 5 10 15 20 25 30
(min)

Percent of Animals Responding to Hair Deflection Stimulus

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during the 30-min period after i.t. STR are presented.

The log dose—response data for i.t. glycine and i.t. betaine were analyzed by linear regression. A modified t test was used to determine if the regression lines had slopes significantly different from 0. Variability associated with single measurements is indicated by standard errors of the mean (SEM). The ED_{50} and 95% confidence interval (CI) of i.t. glycine and i.t. betaine were calculated from their respective dose—response curves (Tallarida and Murray 1987).

**Results**

**General observations following i.t. STR**

Stroking the legs, flanks, lower back, and tail with a cotton-tipped applicator is an innocuous event, which did not elicit cardiovascular or motor responses in the lightly anesthetized rat. However, after i.t. STR (40 μg) the same tactile stimulus triggered a marked increase in HR, an elevation in MAP, and an abrupt motor withdrawal. These abnormal responses to HD could only be evoked at discrete sites, which appeared to correspond to the cutaneous dermatomes innervated by spinal segments near the site of i.t. STR injection (see below).

**Distribution of cutaneous sensitivity following i.t. STR**

The distribution of cutaneous sites sensitive to HD changed with time after STR injection (Fig. 1). There was some caudal spread of sensitivity up to 15 min but no evidence of a rostrally directed increase in allodynia with time. Recovery from STR was complete by 30 min in all affected dermatomes. In some animals, HD-sensitive sites were observed unilaterally. Autopsy of these animals invariably revealed that the tip of the i.t. catheter, and hence the site of STR injection, was laterally positioned in the subarachnoid space on the most responsive side (Fig. 1).
Effects of i.t. glycine and i.t. betaine
The cardiovascular and motor withdrawal responses evoked by HD in STR-treated rats were inhibited by i.t. glycine (Fig. 2) or i.t. betaine (Fig. 3) in a dose-dependent manner. The ED$_{50}$ values (95% CI) for i.t. glycine were 609 (429–865) μg for the HR response, 694 (548–878) μg for the elevation of MAP, and 549 (458–658) μg for the motor withdrawal response. With i.t. betaine, the corresponding values were 981 (509–1889), 1045 (740–1476), and 1083 (843–1391) μg for inhibition of HR, MAP, and motor responses, respectively. Cortical EEG synchrony was not affected by i.t. glycine or betaine, consistent with a spinal locus of action in reversing STR-induced allodynia. Intravenous betaine (2000, 5000, and 10 000 μg) had no significant effect on STR-dependent, HD-evoked cardiovascular and motor responses (data not shown).

Discussion
Segmental localization and time course of STR induced allodynia
HD, applied to the affected dermatomes of i.t. STR treated rats, evoked cardiovascular and motor responses resembling those induced by noxious stimuli without STR. As previously reported (Sherman and Loomis 1994), these evoked responses occurred in the absence of convulsions or spontaneous motor activity, confirming the selective effect of i.t. STR (40 μg) on somatosensory input. In mapping the cutaneous sites exhibiting abnormal sensitivity to HD throughout the STR time course, we have shown that allodynia not only is segmentally distributed but can occur unilaterally in a particular dermatome. Thus, rats with i.t. catheters lying laterally in the spinal subarachnoid space displayed greater sensitivity to HD on the ipsilateral side of i.t. STR injection. These data indicate that i.t. STR induced allodynia is segmentally localized, exhibiting a temporal pattern that is consistent with the lateral and caudal spread of STR in the spinal subarachnoid space. The segmental localization of STR-induced allodynia and the absence of convulsions with this dose of STR are inconsistent with a generalized disinhibition of spinal neurons by i.t. STR. Rather, they strongly suggest that this abnormal sensory state is a localized effect in the dorsal horn of specific spinal segments, which is governed by the lateral and rostrocaudal distribution of STR after i.t. injection.

The changes induced by i.t. STR were also rapid in onset and of short duration (ranging from 15 to 30 min), a time-
Fig. 3. Log dose–response relationship for intrathecal (i.t.) betaine inhibition of responses evoked by hair deflection (HD) after i.t. strychnine (STR). Responses to normally innocuous HD were determined in the presence of i.t. STR (40 μg). (A) The maximum evoked increase in heart rate, (B) the maximum evoked increase in mean arterial pressure (MAP), (C) the duration for which a withdrawal response could be evoked, and (D) the percent synchrony in the EEG were determined following i.t. pretreatment with either saline or one of several doses of betaine. Each point represents the mean ± SEM of 6–10 animals. Least squares regression lines and corresponding 95% confidence intervals (CI; dotted lines) are shown. The horizontal continuous lines and adjacent dotted lines indicate the mean ± 95% CI of all saline treatments (n = 30).

Course profile characteristic of lipophilic drugs such as STR given i.t. (Yaksh and Rudy 1977; Cousins and Mather 1984). Although pharmacokinetic studies of i.t. STR have not yet been conducted, indirect evidence suggests that STR is rapidly cleared from the spinal subarachnoid space. When STR was delivered by continuous i.t. infusion, rates of 5–8 μg/min were required to initiate and maintain allodynia, and a brief interruption (1–2 min) of the infusion led to a rapid decline in the alldynic effect (unpublished observations). Even with high rates of i.t. infusion, a total STR dose of 700 μg could be delivered without inducing convulsions or spontaneous motor activity. In contrast, an i.v. bolus of 300 μg caused convulsions. These observations suggest that STR is rapidly redistributed from cerebrospinal fluid to the periphery, where it is metabolized in the liver to inactive metabolites, and excreted in urine and feces. In this regard, 80% of a 0.5 mg/kg s.c. dose of [3H]STR was eliminated from adult rats within 24 h (Oguri et al. 1989).

It was previously reported that i.t. STR induced allodynia could only be evoked by tactile stimuli (i.e., mechanical pressure) applied to hairy skin of the rat; no allodynia was observed on the tail (Beyer et al. 1988). However, in the present study, motor withdrawal responses were elicited by stroking the tail or hind paws with the cotton-tipped applicator. Beyer et al. (1988) used a 7.5-cm i.t. catheter, whereas ours were 8.5 cm in length. The latter would yield a higher concentration of STR in the sacral region of the spinal cord which innervates the cutaneous dermatomes of the tail. While it is also possible that the tactile-evoked, caudally directed scratching and biting behaviour used by Beyer et al. (1988) may not be as sensitive a measure of allodynia in the tail as the evoked motor withdrawal reflex, our data demonstrate that this effect is not restricted to hairy skin. More likely, it is related to the distribution of STR within the spinal cord after i.t. injection.

I.t. glycine suppresses STR-dependent allodynia

Intrathecal glycine reversed all indices of STR induced allodynia in a dose-dependent manner. These data, and the absence of changes in cortical EEG synchrony following i.t. glycine, indicate that the blockade of spinal glycine receptors is responsible for the somatosensory dysfunction induced by i.t. STR in this model. The doses of i.t. glycine required to antagonize the STR effect were substantially higher (ED<sub>50</sub> values near 600 μg) than other spinally administered drugs that inhibit STR-induced allodynia (ED<sub>50</sub> values < 10 μg) (Yaksh 1989; Sosnowski and Yaksh 1989; Sherman and Loomis 1994). However, considering the relatively low
affinity of STR-sensitive receptors for glycine, the physicochemical properties of glycine, and the efficient uptake mechanisms for glycine in the central nervous system, the need for such high i.t. doses is not unexpected.

Studies using rat spinal synaptosomal membranes have linked STR to a single class of binding sites with an affinity constant in the range of 3–10 nM (Young and Snyder 1974). Glycine has much lower affinity at the glycine receptor, inhibiting STR binding with an IC₅₀ of approximately 6 µM (Johnson et al. 1992). In addition, glycine’s ability to penetrate the spinal cord is impeded by its polarity, and glycine is removed from the site of action by a high affinity uptake system (estimated Kᵦᵦᵦ between 26.5 and 121 µM; Logan and Snyder 1972; Balcar and Johnston 1973). The efficient removal of glycine means that a low basal concentration in spinal tissue (4 µmol/g wet weight; Aprison et al. 1969) and cerebrospinal fluid (60 µM; Semb and Pataslos 1993) is normally maintained, and glycine uptake is not inhibited by STR or depressant amino acids (i.e., γ-aminobutyric acid or β-alanine) (Logan and Snyder 1972; Balcar and Johnston 1973; Fagg and Lane 1979).

Paradoxical STR-like actions of glycine at low i.t. doses may also obligate the use of higher doses to inhibit STR-induced allodynia. Behavioural allodynia has been reported with i.t. glycine at doses of 5–400 µg (Beyer et al. 1985). Vocalization, in response to light stroking of the hair, was not as prevalent nor as intense as that observed after i.t. STR, and the allodynic effect gradually disappeared as the dose of i.t. glycine was increased to 400 µg. A subsequent study from the same laboratory found no sensory or motor manifestations with 400 µg of i.t. glycine, a dose that significantly reduced allodynia to i.t. STR (Beyer et al. 1988). These results, using conscious behaving rats, are in agreement with the dose–response data for i.t. glycine in our urethane-anesthetized model.

I.t. betaine suppresses STR-dependent allodynia

Betaine (N,N,N-trimethylglycine), an endogenous glycine derivative and putative glycine receptor agonist, also antagonized the cardiovascular and motor withdrawal responses evoked by HD in STR-treated rats. These results are consistent with the effect of i.t. glycine described above, and provide additional evidence that STR-induced allodynia results from the blockade of spinal glycine receptors.

In a previous study, Beyer et al. (1988) reported that i.t. betaine (800 µg) selectively blocked the convulsive effects but not the skin hyperalgesia or other sensory manifestations of i.t. STR in the rat. Using dose–response analysis, we found no difference in the effect of betaine on sensory-evoked cardiovascular or motor responses in STR-treated rats. Although a nonconvulsive dose of STR (40 µg i.t.) was specifically chosen for the present study, our data clearly indicate that i.t. betaine does not selectively affect efferent motor pathways evoked by HD in the spinal cord of STR-treated rats.

As with glycine, the doses of i.t. betaine required to prevent STR-induced allodynia were large. However, unlike glycine, a high affinity uptake system has not been described for betaine. Moreover, betaine, N,N-dimethylglycine, and sarcosine (N-methylglycine) were equipotent in reducing STR-induced seizures and death (Freed 1985), highlighting their ability to penetrate the brain and spinal cord, and their lack of structural specificity in blocking the actions of STR. This is in marked contrast with the stringent structural requirements for glycine receptor agonists (Young and Snyder 1973; Drummmond et al. 1989). It is therefore unclear whether betaine has a direct action at the STR binding site on the glycine receptor.

Receptor binding studies have not been carried out to determine if betaine binds directly to STR-sensitive glycine receptors. However, a structurally similar glycine derivative, N,N-dimethylglycine, neither reduced nor potentiated the depressant effects of glycine on cat spinal interneurons (Curtis et al. 1968). Alternatively, betaine may be a produrg, yielding the active product, glycine (Barak and Tuma 1983). Betaine is metabolized in the liver to N,N-dimethylglycine, sarcosine (N-methylglycine), and ultimately glycine (Barak and Tuma 1983), but the extent to which this metabolic conversion occurs in the central nervous system is unknown. The peripheral metabolism of betaine appears to be of little importance in the reversal of STR-dependent allodynia since i.v. betaine, in doses up to 10 mg, had no significant effect. The high doses of i.t. betaine required in the present experiments suggest that competition between the unmetabolized betaine molecule and STR at glycine receptors is unlikely to be its primary mechanism of action. Rather, it may reflect the limited rate of glycine release from betaine in the central nervous system, or a nonspecific effect of betaine to inhibit STR blockade.

Summary

The present study demonstrates that i.t. STR induced allodynia is segmentally localized and appears to be related to the distribution of STR in the spinal subarachnoid space. All sensory-evoked, STR-dependent responses were dose dependently inhibited by i.t. glycine or the glycine derivative betaine. These results support the hypothesis that removal of spinal glycinergetic modulation from low threshold afferent input results in tactile-evoked allodynia.

References


