Coadministration of Intrathecal Strychnine and Bicuculline Effects Synergistic Allodynia in the Rat: An Isobolographic Analysis

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ABSTRACT

Tactile allodynia can be modeled in experimental animals by acutely blocking spinal glycine or GABA<sub>A</sub> receptors with intrathecal (i.t.) strychnine (STR) or bicuculline (BIC), respectively. To test the hypothesis that glycine and GABA effect cooperative (supra-additive) inhibition of touch-evoked responses in the spinal cord, male Sprague-Dawley rats, fitted with chronic i.t. catheters, were used. Following i.t. STR, BIC, or STR + BIC, hair deflection evoked cardiovascular (increased blood pressure and heart rate), motor (scratching, kicking and rippling of the affected dermatomes), and cortical encephalographic responses. Hair deflection was without effect in i.t. saline-treated rats. Isobolographic analysis of STR (ED<sub>50</sub> = 25.1–36.9 μg), BIC (ED<sub>50</sub> = 0.5–0.6 μg), and BIC:STR combination (ED<sub>50</sub> = 0.026–0.034:2.6–3.4 μg) dose-response curves confirmed a supra-additive interaction between BIC and STR in this model. BIC-allodynia was reproduced by i.t. picrotoxin. Pretreatment with i.t. scopolamine, or i.t. muscarine had no effect. STR-allodynia was dose dependently inhibited by i.t. muscimol but not baclofen. The results of this study indicate that 1) glycine and GABA effect cooperative inhibition of low-threshold mechanical input in the spinal cord of the rat; and 2) BIC-allodynia arises from the blockade of GABA<sub>A</sub> receptors and is unrelated to any secondary anticholinesterase activity. The allodynic state induced by the blockade of glycine or GABA receptors is clearly exacerbated by the removal of both inhibitory systems. Their combined loss after neural injury may explain the exaggerated sensitivity to and subsequent miscoding of tactile information as pain.

Convergent lines of evidence suggest that glycine and γ-aminobutyric acid (GABA) play important roles in the spinal processing of low-threshold mechanoreceptive input (Curtis et al., 1968; Yaksh, 1989; Todd, 1990; Todd and Sullivan, 1990; Sherman and Loomis, 1994; Sorkin et al., 1998). Glycinergic neurons in laminae II and III receive a major monosynaptic input from myelinated primary afferent fibers in the rat (Todd, 1990). GABA and glycine are colocized in interneurons in spinal laminae I–III (Todd and Sullivan, 1990; Mitchell et al., 1993; Todd et al., 1996) and are coreleased from the same interneurons (Jonas et al., 1998). Furthermore, spinal glycine- and GABA<sub>A</sub> receptors are localized on the same postsynaptic membranes (Mitchell et al., 1993; Todd et al., 1996), suggesting that GABA and glycine work together to effect sensory modulation.

Indeed, the blockade of spinal glycine- or GABA<sub>A</sub> receptors yields an abnormal state suggestive of allodynia (a condition in which normally innocuous stimuli produce severe pain). Thus, intrathecal (i.t.) bicuculline (BIC; GABA<sub>A</sub> antagonist) or strychnine (STR; glycine antagonist) produces a reversible state in which light touch evokes nociceptive-like vocalization, biting, and escape behavior in conscious rats and mice, and tactile-evoked autonomic, motor, and neurochemical responses in anesthetized rats (Yaksh, 1989; Minami et al., 1994; Sherman and Loomis, 1994; Milne et al., 1996; Onaka et al., 1996). Moreover, genetic variants such as the Poll Hereford calf (Gundlach et al., 1988) and the spastic mouse (White and Heller, 1982), which exhibit up to a 10-fold decrease in STR binding in the spinal cord, display exaggerated sensitivity to even modest cutaneous stimulation. These animal data are consistent with reports of pronounced hypersensitivity and pain to light touch in humans during STR intoxication (Arena, 1979), suggesting that glycine, and presumably GABA, are essential in the modulation of low-threshold mechanical input.

These observations are supported by previous electrophys-

ABBREVIATIONS: GABA, γ-aminobutyric acid; i.t., intrathecal; BIC, bicuculline; STR, strychnine; IPSP, inhibitory postsynaptic potential; EEG, electroencephalograph; HD, hair deflection; MAP, mean arterial pressure; HR, heart rate; CI, confidence interval; BP, blood pressure; AP-5, 2-amino-5-phosphonoventanoic acid; l-AP4, l(-)-2-amino-4-phosphonobutyric acid; l-AP3, l(-)-2-amino-3-phosphonopropionic acid.
ological data. Iontophoretic delivery of glycine and GABA diminished 1) the responsiveness of dorsal horn neurons to light tactile stimulation in cats; 2) the size of their cutaneous receptive fields (Ziegglansberger and Hertz, 1971); and 3) the glutamate- and pinch-evoked firing of the spinohalamic tract neurons in monkeys (Wilcockson et al., 1984). Conversely, STR or BIC in the lumbar spinal cord diminished the inhibition elicited by natural or electrical stimulation of low-threshold afferent fibers of the cat (Game and Lodge, 1975), and increased neuronal activity evoked by low-threshold afferent input in cats and monkeys (Khayyat et al., 1975; Yokota et al., 1979). The effect of BIC on the electrophysiological activity of rat spinal neurons is dose-dependent (Sorkin et al., 1998). The blockade of inhibitory postsynaptic potentials (IPSPs) with BIC or STR or both enhanced the excitatory postsynaptic potentials of rat ventrolateral medullary neurons (Lin et al., 1998). To the extent that spinal GABA and glycine are necessary to balance the degree of excitation of convergent neurons, the removal of these inhibitory systems would strengthen the synaptic connections between non-nociceptive fibers and pain-signaling pathways. This could result in the miscoding of an innocuous stimulus as pain.

At the cellular level, there are important differences between GABA- and glycine-mediated inhibition. For example, the time course of IPSPs elicited by GABA and glycine are distinct. Short IPSPs (mean latency 3.6 ms, half-decay 11 ms) are mediated by glycine, whereas the longer IPSPs (mean latency 3.7 ms, half-decay 42 ms) are GABA mediated (Shimamura and Nishi, 1995). Thus, glycine and GABA appear to have distinct but complementary effects on spinal neurons. There are also important differences in the spinal pharmacology of allodynia induced by glycine- and GABA antagonists. STR-allodynia in mice was blocked by the 1) nitric oxide synthase inhibitor Nω-nitro-l-arginine methyl ester; 2) N-methyl-d-aspartate receptor antagonists AP-5 and ketamine; 3) non-N-methyl-d-aspartate receptor antagonist 6-cyano-2,3-dihydroxy-7-nitroquinoxaline; and 4) guanylate cyclase inhibitor methylene blue (Onaka et al., 1996). STR-allodynia was unaffected by the metabotropic receptor antagonists l-AP3 and l-AP4 (Onaka et al., 1996). In contrast, BIC-allodynia was blocked by l-AP3, l-AP4, and methylene blue but unaffected by Nω-nitro-l-arginine methyl ester, 6-cyano-2,3-dihydroxy-7-nitroquinoxaline, AP-5, and ketamine (Onaka et al., 1996).

If GABA acting at spinal GABA_A receptors, and glycine acting at STR-sensitive glycine receptors, negatively modulate low-threshold transmission through distinct but complimentary mechanisms, then the removal of both inhibitory systems should exaggerate an allodynic state. This outcome and the interaction between glycine and GABA in the spinal cord have not been determined. In the present study, we investigated the combined effects of i.t. STR and BIC using isobolographic analysis. We also verified the role of GABA_A receptors in this model.

Materials and Methods

Animals. Male, Sprague-Dawley rats (300–490 g at the time of the experiments) were obtained from the Vivarium, Animal Care Services, Memorial University of Newfoundland (St. John’s, Canada). Animals were housed in the Animal Care Facility, with a 12-h dark/light cycle, a room temperature of 22°C, and free access to food and 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.

Procedures. Under halothane anesthesia, rats were fitted with i.t. catheters prepared from stretched polyethylene tubing (PE-10 pulled to ~1.5 × the original length). The catheters, filled with sterile saline (Astra Pharma Inc., Mississauga, Canada), were inserted through the cisterna magna into the spinal subarachnoid space, and guided 8.5 cm caudally terminating near the L1-L2 segment. A fixed loop near the rostral end of the catheter was sutured to the overlying muscle to secure the catheter and the incision closed. The rostral tip was externalized on the top of the head and sealed with a stainless steel plug. Animals recovered for at least 4 days before experimentation and only those exhibiting normal motor, grooming, and feeding behavior were used.

On the day of the experiment, the left jugular vein was cannulated under halothane anesthesia. Halothane was then discontinued and anesthesia was maintained using i.v. urethane (1.1 g/kg infused over 10–15 min as the anesthetic effect of halothane declined). Body temperature was maintained at 37°C with a thermostatically regulated blanket. The left carotid artery was cannulated for continuous monitoring of blood pressure and heart rate as previously described (Sherman and Loomis, 1994, 1995).

A light of plane anesthesia, defined by the cortical EEG pattern (high-amplitude synchronous activity present for not more than 60% of the time (Sherman and Loomis, 1994), was maintained. Throughout the experiment, anesthesia was also assessed by observing the corneal reflex responses, whisker movements, or responses to light pinch and supplemented with i.v. urethane as required.

Hair deflection was used as the innocuous stimulus. The hair on the legs, flanks, and lower back was sequentially brushed with a cotton-tipped applicator using an oscillating motion (rate of 1–2/s; 2-min stimulus train applied at 3-min intervals). Brushing was done with no more force than required to move the applicator through the hair such that only the pelage was disturbed.

Drugs. Bicuculline methiodide and strychnine hemisulfate were obtained from Sigma Chemical Co. (St. Louis, MO). Muscimol hydrobromide and R(+)-baclofen hydrochloride were obtained from Research Biochemicals International (Natick, MA). Muscarine chloride, picrotoxin, and scopolamine hydrobromide were obtained from Aldrich Chemical Co. (Milwaukee, WI). All drugs were dissolved in 0.9% saline (Astra Pharma Inc., Mississauga, Canada) and administered i.t. in a volume not exceeding 10 µl. Drug solutions were flushed through catheter with 10 µl of saline.

Experimental Protocols. Dose-response curves for BIC and STR + BIC were determined in separate groups of rats. Each animal received i.t. saline, followed 10 min later by i.t. BIC (0.1, 0.25, 0.5, and 0.75 µg) or BIC:STR (0.001:0.1, 0.005:0.5, 0.0075:0.75, 0.01:1, and 0.01:10 µg). A fixed molar ratio of 1:133 was selected from the estimated ED50 values for BIC and STR. The STR dose-response curve (data not shown) was constructed as previously published (Sherman and Loomis, 1994). This curve has been generated several times in our laboratory and has proven highly reproducible. The HD stimulus was applied at 5-min intervals until evoked cardiovascular/motor responses were no longer observed (approximately 30–45 min after BIC/STR injection). The total period of time that motor responses could be evoked by HD was also determined. The percentage of synchrony was calculated by determining the number of 1-min intervals with a synchronous EEG (determined visually) and expressing this as percentage of the experimental time.

Effect of Intrathecal Muscimol and Baclofen on STR-Alloodynia. To establish the control responses to STR + HD (e.g., in absence of any other drug treatment), each rat received i.t. vehicle followed 10 to 15 min later by i.t. STR (40 µg). This dose of STR elicits optimal allodynia without convulsive activity in lightly anesthetized rats (Sherman and Loomis, 1994). Approximately 1 h later, rats were pretreated with i.t. muscimol (0.1, 0.5, 1, and 2.5 µg) or...
baclofen (1, 5, and 10 µg) followed 15 min later by i.t. STR (40 µg). Hair deflection was then applied at 5-min intervals. All animals received multiple drug doses. The order of dosing was always from low to high to reduce the possibility of a carry-over effect and thus, the recovery time. No more than three doses were administered to the same animal. Preliminary time course studies indicated that a 15-min pretreatment time was optimal for i.t. drug administration and that 1.5 h between doses was sufficient for complete recovery from even the highest doses.

Data Analysis. All cardiovascular data are presented as the maximum change in MAP (=systolic blood pressure +½ pulse pressure) and HR evoked by HD relative to the immediate (1-min) prestimulus control period. Dose-response data were analyzed using regression analysis and ED₅₀ and 95% confidence interval (CI) values determined. Variability associated with single measurements is indicated by the S.E.M., whereas variability associated with blocks of data is indicated by the pooled 95% CI. Significant differences among the baclofen-treated groups were determined using completely randomized one-way ANOVA and the Newman-Keuls test. Methods of data analysis were based on a general text (Tallarida and Murray, 1987).

Results

Stroking the hair on the legs, flanks, and lower back of the lightly anesthetized animal with a cotton tip applicator was without effect in i.t. saline-treated animals. An identical stimulus applied to rats pretreated with i.t. STR and/or BIC evoked a progressive rise in HR and BP that persisted beyond the duration of the HD stimulus. These responses were accompanied by abrupt motor responses (scratching activity at the site of stimulation, kicking of the hind limbs, and muscular contraction in the affected dermatomes) and desynchrony of the EEG. Normalization of the EEG (return to a synchronous pattern), which occurred 1 to 2 min after the discontinuation of the HD stimulus, coincided with recovery of baseline BP and HR. The magnitude of these HD-evoked cardiovascular responses were dependent on the dose of BIC or the BIC + STR combination (Figs. 1 and 2). The cardiovascular and motor responses were only evoked by HD at discrete sites corresponding to dermatomes innervated by spinal segments near the site of STR and/or BIC injection. BIC-allodynia lasted up to 45 min following the injection of 0.75 µg compared with STR-allodynia, which persisted up to 30 min at a dose of 40 µg. At low doses, the STR:BIC combination exhibited a time course profile similar to that of STR-allodynia. At high doses, the combination resembled that of BIC-allodynia.

Unlike i.t. STR, i.t. BIC also elicited spontaneous (non-evoked) increases in BP and HR, and motor responses (kicking and scratching of the affected area) that lasted up to 15 min after injection. These were especially noticeable at the highest dose (0.75 µg). In cases where spontaneous responses lasted longer than 5 min, the HD stimulus was withheld until the spontaneous rise in BP and HR began to normalize. STR and BIC exhibited a significant difference in potency in this preparation. As shown in Table 1, the ED₅₀ values for i.t. BIC were 0.5 µg for MAP and 0.6 µg for HR. In contrast, the potency of i.t. STR was 25 µg for MAP and 37 µg for HR. The ED₅₀ values for BIC:STR combination were 26 mg:2.6 µg for MAP and 34 ng:3.4 µg for HR (Table 1). Isobolographic analysis revealed a significant supra-additive interaction between i.t. BIC and STR in this model (Fig. 3).

The allodynic effect of BIC was not mimicked by i.t. muscimole (2–4 µg, n = 3) nor was it affected by pretreatment with i.t. scopolamine (acetylcholinesterase inhibitor, 30 µg, n = 3) (data not shown). In the presence of i.t. picrotoxin (2 µg, n = 3), HD evoked cardiovascular and motor responses comparable to those of BIC (0.25 µg) (Table 2). Weak responses were also observed in absence of tactile stimulation (data not shown).

Intrathecal muscimol (0.1, 0.5, 1, and 2.5 µg), given 15 min before STR (40 µg), dose dependently inhibited all indices of STR-allodynia (Fig. 4). The ED₅₀ values and 95% CI for i.t. muscimole were 0.5 µg (0.4–0.7) for MAP, 0.5 µg (0.3–0.7) for HR, and 0.4 (0.3–0.6) for duration of motor responses. This antiallodynic effect was accomplished without a change in the percentage of synchrony of the EEG, which remained below the 60% cut-off. Baseline cardiovascular responses were also unaffected by muscimole up to 2.5 µg i.t. (data not shown). In contrast, baclofen (up to 10 µg i.t.) failed to inhibit STR-allodynia (Table 4). However, motor responses to HD were significantly attenuated by i.t. baclofen (*p < 0.01). Indeed, one rat receiving the 1-µg dose, and all rats receiving ≥5 µg exhibited reversible hind limb paralysis as determined by the absence of the pinch-evoked motor reflex.

Discussion

Strychnine- or Bicuculline-Induced Alldynia. Hair deflection, applied to the affected dermatomes of rats pretreated with i.t. STR and/or BIC, evoked a marked cardiovascular and motor response, and desynchrony of EEG sug-
gestive of allodynia. These data are consistent with previous studies (Yaksh, 1989; Sherman and Loomis, 1994) and indicate that robust allodynia can be selectively induced with i.t. STR and/or BIC in animals whose somatosensory systems are otherwise normal. Interestingly, the ED50 of i.t. BIC was approximately 70 times lower than that of i.t. STR. There are a number of possibilities to explain this difference. The first is the more widespread distribution of GABA-containing neurons throughout the dorsal gray compared with glycine-containing elements (Todd and Sullivan, 1990). For example, of the total neurons counted in lamina I–III, approximately 35% were GABA immunoreactive, whereas only 17% were glycine immunoreactive (Todd and Sullivan, 1990; Laing et al., 1994). First, considering the fact that virtually all glycine immunoreactivity in lamina I–III is restricted to neurons that also contain GABA, these results suggest that only about 50% of total GABA-immunoreactive neurons cocontain glycine (Todd and Sullivan, 1990). Second, BIC-allodynia is longer lasting (up to 40 min) compared with STR-allodynia (30 min). This suggests a difference in the kinetics (clearance) of STR and BIC from the cerebrospinal fluid. In fact, the allodynic effects of STR disappeared rapidly (1–2 min) after discontinuation of the spinal infusion of STR (5–8 µg/min) in the rat (Sherman, 1994). However, a difference in clearance only partially explains the difference in the potency of BIC since this difference persists when STR or BIC is applied topically to the surface of the spinal cord (Zhang et al., 2001). The difference in potency may also reflect differences in the mechanism of receptor blockade. Unlike STR,
SEM of 3 to 14 animals (N values shown in parentheses). The synaptic pool. Intrathecal BIC, but not STR, has been shown to increase the tonic release of excitatory amino acids in the spinal cord of the rat (54% increase above baseline in the first 10 min after injection) (Ishikawa and Yaksh, 1996). This spontaneous activity could also explain the exaggerated responses observed in the absence of tactile stimulation.

Selective Role of GABAA Receptors in the Induction of Allodynia. The i.t. administration of cholinergic agonists has been shown to induce spontaneous responses (i.e., increased pressor responses, tremor, scratching, tail biting, and chewing responses in conscious rats) similar to those evoked by HD in experimental allodynia (Magri and Buccafusco, 1988). In this regard, BIC is known to possess weak, reversible anticholinesterase activity, although this effect is normally observed in vitro at the concentrations of >30 μM (Svenneby and Roberts, 1973). GABAA receptor blockade is observed at concentrations of <3 μM (Olsen et al., 1976). To exclude the possible role of acetylcholinesterase inhibition in BIC-allodynia, we examined the effect of i.t. 1) muscarine, 2) scopolamine, and 3) picrotoxin. Given that scopolamine failed to block the allodynic effect of BIC, and that i.t. muscarine had no allodynic activity, BIC-allodynia appears to be due to the blockade of GABAA receptors. This conclusion is further supported by the allodynia-like behavior induced by i.t. picrotoxin, which blocks the chloride channel comprising the GABAA receptor-channel complex. Picrotoxin lacks anticholinesterase activity (Svenneby and Roberts, 1973).

Supra-Additive Interaction between STR and BIC in Allodynia. From the discussion described above it is clear that i.t. BIC and STR each elicit acute and selective allodynia in the rat. This observation and qualitative similarity of their effects indicate the importance of glycine and GABA in the modulation of low-thresholdafferent input. In combination, the doses of BIC and STR required to induce allodynia were 10 times lower than their individually effective doses. Isobolographic analysis clearly indicated a supra-additive interaction between STR and BIC. Such an interaction is consistent with the fact that 1) GABAA and glycine receptors effect the opening of distinct chloride channels to hyperpolarize neurons (Bormann et al., 1987); 2) GABAA and glycine receptors are co-contained on the same postsynaptic membranes in the spinal dorsal horn (Todd et al., 1996); 3) glycine and GABA appear to be coreleased from the same interneurons (glycine immunoreactivity is virtually restricted to neurons that also exhibit GABA immunoreactivity in the laminae I–III of the dorsal horn) (Todd and Sullivan, 1990; Mitchell et al., 1993); 4) vesicular transporters at inhibitory synapses accept both glycine and GABA as substrates (Burger et al., 1991; Sagen et al., 1997); and 5) GABAA and glycine-mediated inhibition of single spinal cord neurons have unique time courses (Game and Lodge, 1975; Baba et al., 1994; Yoshimura and Nishi, 1995).

Although the exact role and significance of glycine- and GABAA inhibition remains to be determined, it has been suggested that the STR-sensitive IPSPs may be important in limiting the firing of the neurons and curtailing the amplitude and the ability of the EPSP to generate an action potential (Yoshimura and Nishi, 1995). In contrast, BIC-sensitive IPSPs, which develop more slowly and have a longer duration, may be effective in preventing longer lasting repetitive activation (Yoshimura and Nishi, 1995). Thus, glycine- and GABA-mediated cotransmission could support the precise regulation of the time course of postsynaptic conductance.

**TABLE 3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MAP</th>
<th>HR</th>
<th>MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle-control (14)</td>
<td>13.4 ± 1.6</td>
<td>20.7 ± 1.9</td>
<td>25 ± 2.0</td>
</tr>
<tr>
<td>Baclofen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.8 ± 4.9</td>
<td>33.3 ± 13.0</td>
<td>6.7 ± 3.3&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 μg (3)</td>
<td>25.4 ± 5.0</td>
<td>40 ± 8.4</td>
<td>Absent</td>
</tr>
<tr>
<td>5 μg (4)</td>
<td>22.3 ± 4.8</td>
<td>49 ± 9.4</td>
<td>Absent</td>
</tr>
<tr>
<td>10 μg (5)</td>
<td>22.3 ± 4.8</td>
<td>49 ± 9.4</td>
<td>Absent</td>
</tr>
</tbody>
</table>

MD, duration of motor responses.

<sup>a</sup> Baclofen was injected 15 min before STR. Data are expressed as the mean ± SEM of 3 to 14 animals. (N values shown in parentheses).
by the relative amount of glycine and GABA released from the presynaptic interneuron. The combined loss of GABA- and glycine-containing interneurons would disrupt the precise modulation of somatosensory input. The apparently complementary effects of glycine and GABA on somatosensory input are consistent with the inhibition of STR-allodynia by i.t. GABA_B agonists. Intrathecal muscimol dose dependently inhibited STR-allodynia in lightly anesthetized rats. In contrast, i.t. baclofen failed to suppress the abnormal responses to HD in presence of spinal STR; even at doses yielding pronounced motor dysfunction (>1 µg). These data are in agreement with previous reports demonstrating the lack of effect of 1) i.t. baclofen against STR-allodynia in conscious rats (Yakh, 1989); and 2) intra-arterial CGP 35348 (GABA_B antagonist, 60 mg/kg) on the spontaneous activity of hamstring flexor α-motoneurons, the touch evoked-firing of spinal neurons, or their touch threshold in the rat (Sivilotti and Woolf, 1994).

The results of the present study have implications for our understanding of allodynia. If glycine and GABA interneurons are vulnerable to excitotoxic death after neural injury, then the combined loss of glycine and GABA could explain the exaggerated sensitivity to and central nociceptive stimulation in clinical allodynia. In this regard, the combined blockade of glycine- and GABA_A receptors would be a more appropriate spinal disinhibitory model than either one alone.

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