

Intravenous Lidocaine Inhibits Visceral Nociceptive Reflexes and Spinal Neurons in the Rat

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Background: Systemically administered local anesthetics and other sodium channel blockers produce analgesia in patients with hypersensitivity disorders. To assess whether these agents have a role in the treatment of visceral pain, the present study examined the effects of intravenous lidocaine on neuronal and reflex responses to colorectal distension.

Methods: In decerebrate, cervical spinal cord-transected male rats, the lumbosacral spinal cord was exposed by a laminectomy. Dorsal horn neurons demonstrating excitatory responses to colorectal distension were identified using microelectrodes. Sequential doses of lidocaine were administered intravenously. In chronically instrumented, unanesthetized rats, visceromotor responses, pressor responses, and increases in heart rate were elicited by colorectal distension and sequential doses of lidocaine.

Results: Intravenous lidocaine dose-dependently inhibited visceromotor and cardiovascular reflexes and the evoked and spontaneous activity of neurons excited by colorectal distension. There were statistically greater effects on one of the neuronal subgroups (sustained neurons) than on another subgroup (abrupt neurons.)

Conclusions: Intravenous lidocaine had dose-dependent, inhibitory effects on two spinal neuronal populations excited by colorectal distension and dose-dependently inhibited reflex responses to the same stimulus. This suggests there may be utility of sodium channel blockers in the treatment of pain of visceral origin. (Key words: Dorsal horn; pseudotachyarrhythmia; sodium channel blocker visceromotor.)

THE intravenous administration of local anesthetics and other sodium channel blockers has been demonstrated to have analgesic actions in numerous painful conditions,¹ in particular, disorders associated with hypersen-

sitivity, such as fibromyalgia,² or neuropathic pains,³ such as those following stroke,⁴ secondary to antitumor immunotherapy⁵ or with diabetic neuropathy.⁶ Intravenous lidocaine and other sodium channel blockers have also been demonstrated to have inhibitory effects on neurophysiologic responses evoked by A δ and C fibers⁷⁻⁹ as well as thermal stimuli.¹⁰ Recent experimental studies in humans have demonstrated little effect of intravenous lidocaine on normal pain thresholds but profound effects on hyperalgesia-related phenomena.^{11,12} It has been proposed that many visceral pains may represent similar hypersensitivity states.¹³ To determine whether there may be a role for sodium channel blockers in the treatment of visceral pain, an investigation of the effect of lidocaine on reflex and neuronal responses to repeated gut distension was undertaken.

Colorectal distension (CRD) has been used extensively in studies in humans to produce reports of discomfort and pain¹⁴ and has also been used in rats, rabbits, horses, cats, dogs, and primates to evoke vigorous physiologic, neuronal, and behavioral responses interpreted as nociceptive responses.^{15,16} Repeated presentation of a distending stimulus leads to an initial sensitization process, but after 7-10 distensions, neuronal and reflex responses are stable.^{14,16} Multiple sites within the central nervous system are activated by CRD. At least two spinal neuronal populations encode for CRD in an excitatory, graded fashion and can be distinguished from each other in several ways.¹⁷ One group, sustained neurons, are characterized by the presence of a sustained afterdischarge for 4-240 s after the termination of a phasic distending stimulus. The other group, abrupt neurons, have an abrupt cessation of activity immediately after the termination of the distending stimulus. Both abrupt and sustained neurons are excited by noxious cutaneous stimuli presented to same-segmental, receptive fields (e.g., the perineum), but only abrupt neurons are reliably inhibited by the presentation of noxious stimuli to distant parts of the body (i.e., subject to counterirritation). Sustained neurons are not similarly inhibited.¹⁸ Activity of neurons excited by CRD has been inhibited by intrave-

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nous morphine,^{19,20} clonidine,²⁰ and κ opioid receptor agonists,²¹ with differential effects of these agents on the two neuronal populations. The present study extended these previous studies by investigating the effects of intravenous lidocaine on abrupt and sustained neurons within the L6–S2 spinal cord segments and on reflex responses to CRD.

Materials and Methods

The methodology of this study was approved by the local animal care utilization review board. All studies were performed in male, Sprague-Dawley rats. To limit possible interactions with other anesthetics, the electrophysiologic studies were performed in the absence of other anesthesia in a cervical spinal cord-transected decerebrate preparation. Reflex studies require an intact animal because the cardiovascular and reflex responses to CRD are absent in spinalized preparations but vigorous in intact, unanesthetized rats. As such, the effect of intravenous lidocaine reflex responses to CRD were examined in chronically instrumented, intact unanesthetized rats.

Colorectal Distension

Phasic, constant-pressure CRD was produced by inflating with air a 7–8-cm long flexible latex balloon inserted transanally into the descending colon and rectum. The balloon had a diameter greater than the distended gut so that the continuously measured intraluminal pressure (monitored directly *via* an in-line, low-volume pressure transducer) was an accurate measure of the intensity of CRD. In the electrophysiologic and cardiovascular reflex experiments, CRDs (80 mmHg, 20 s) were supplied at 4-min intervals after 7–10 initial CRDs. This protocol results in stable cardiovascular reflex and neuronal unit responses to CRD throughout the course of an experiment.^{16,17} For the visceromotor reflex experiments, the pressure within the distending balloon was presented in a “ramped” fashion, with increasing pressures (0–80 mmHg) at a rate of approximately 20 mmHg/s. This protocol also results in a reliable visceromotor reflex response to CRD at a stable intraluminal pressure throughout the course of an experiment.¹⁶

Electrophysiologic Preparation

Rats were deeply anesthetized with inhaled halothane (2–5%) in oxygen. Tracheal, carotid arterial and jugular venous cannulae were inserted. The cervical spinal cord

was exposed at the level of the atlanto-occipital joint, fully transected, and the entire brain was mechanically pithed with a forceps. Rats were then ventilated with air-oxygen and allowed to recover ≥ 4 hours, at which time they demonstrated vigorous withdrawal reflex responses to tail pinch but no spontaneous movements. Paralysis was then established with pancuronium bromide (0.2 mg/h intravenously). Blood pressure was continuously monitored, and rats were kept at physiologic temperatures using overhead lamps. Normal saline was administered as needed to prevent hypovolemia. The lumbosacral spinal cord was exposed by laminectomy, and the rats were suspended from thoracic and lumbar vertebral clamps. The dura mater was carefully cut, and skin flaps were arranged to allow for formation of a protective bath of warm paraffin oil over the exposed spinal cord.

Neuronal Characterization

Tungsten microelectrodes were used for single-unit recordings 0–1.0 mm lateral to midline, 0.1–1.0 mm ventral to the spinal cord dorsum. Brief, phasic CRDs were used as the primary search stimuli. Isolated units that were reliably and reproducibly excited (responses $\pm 20\%$ from the mean) by CRD (80 mmHg, 20 s) on three consecutive trials were characterized further. Responses (excitatory/inhibitory) to cutaneous inputs were determined using the following stimuli: brush with a cotton-tipped applicator (nonnoxious mechanical), pinch with rat-tooth forceps at sufficient intensity to produce pain in the investigator (noxious mechanical), and a thermal contact probe heated to $> 50^\circ\text{C}$ (noxious heat). The effect on spontaneous activity of a 5-s application of a vascular clamp to the tail or forepaw (a nonsegmental “distant” noxious stimulus) was determined in all units.

To quantify neuronal responses, units were displayed oscillographically for continuous monitoring, discriminated conventionally from background, converted into uniform pulses, and saved by computer as peristimulus-time histograms. Spontaneous activity was determined as the average number of action potentials per second in the 10-s period before the onset of CRD. Total activity was determined as the total number of action potentials during the 20-s CRD stimulus. Evoked activity was calculated as the difference between the total activity and the calculated spontaneous activity (mean rate in $\text{Hz} \times 20$).

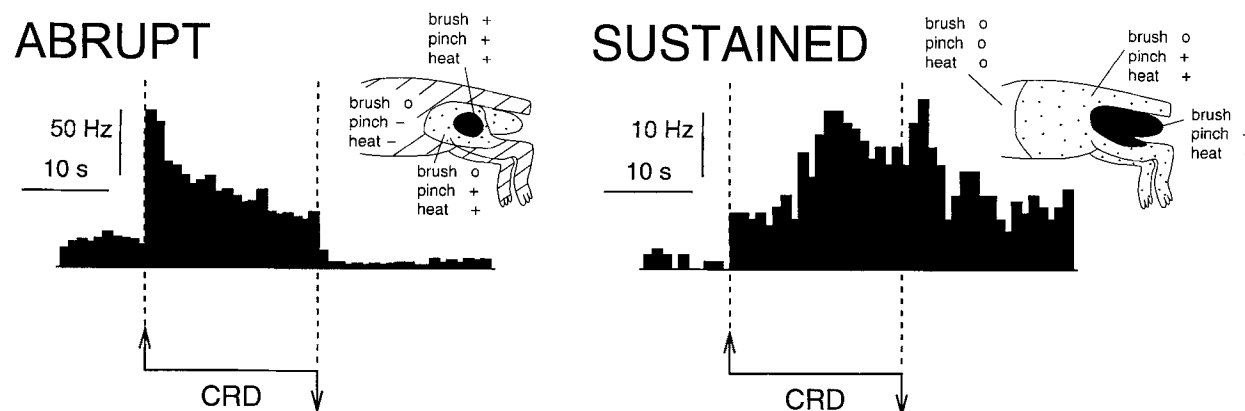


Fig. 1. Typical examples of an abrupt (left) and a sustained (right) neuron. Peristimulus-time histograms (1-s bins) are displayed, demonstrating response to colorectal distension (CRD; 80 mmHg, 20 s). Convergent cutaneous receptive fields for the same neurons are displayed in adjacent cartoon form. Brushing of the skin, pinching with forceps, and applying a hot probe ($> 50^{\circ}\text{C}$) were used as cutaneous stimuli: + = excitatory response; - = inhibitory response; o = no response.

Reflex Response Preparation

Rats were anesthetized with inhaled halothane (2–5%) in oxygen. Using sterile technique, arterial and/or venous cannulae were placed in femoral vessels and tunneled subcutaneously to the nape of the neck, where they were externalized. Wounds were closed, and rats were allowed to recover for 3 days before additional testing. On the day of testing, rats were briefly anesthetized with halothane, the balloon assembly was inserted transanally, and the connecting catheter was taped to the base of the tail. At the same time, the chronic vascular catheters were accessed. In eight rats, arterial blood pressure was measured continuously using a low-volume pressure transducer and recorded on a strip chart. Heart rates were measured by analysis of the blood pressure tracing. These rats were allowed to recover from anesthesia and crawl within a dark glove, where they remained for the duration of the experiment. Cardiovascular responses to CRD (80 mmHg, 20 s) were evoked every 4 min for the duration of the experiment. In five rats, visceromotor responses to CRD were observed and quantified as the visceromotor threshold, the minimal intracolonic pressure necessary to evoke a reflex contraction of the abdominal/hind limb musculature. Visceromotor thresholds were determined every 4 min throughout the course of the experiment.

Intravenous Drug Protocol

Reflex and neuronal responses to CRD were determined every 4 min with two “baseline” trials performed before administration of any drug. Sequential doses of lidocaine hydrochloride (0.25, 1, and 4 mg/kg; Abbott Laboratories, Chicago, IL) were administered intrave-

nously at 16-min intervals beginning 1 min before a CRD stimulus. These doses of lidocaine were selected based on preliminary experiments and the frequent clinical use of doses of lidocaine in the 1–5-mg/kg range.¹ Previous studies using intravenous saline as a control have demonstrated no effect of that treatment.¹⁶

Statistical Analysis

Descriptive statistics are reported as mean \pm SD. Statistical comparisons were made using a repeated measures analysis of variance. Comparisons with baseline data were made using a paired *t* test. $P < 0.05$ was considered significant in all tests. To combine data, values of each measure (e.g., evoked activity) were normalized by dividing individual values by the mean of that measure determined on the two trials that occurred before the administration of any study drug. Changes in activity were limited to 100% (decrease or increase).

Results

Neuronal Sample

A total of 28 neurons in the dorsal horn of the L6–S2 spinal segments of 28 rats were identified and characterized further, and the effects of intravenous lidocaine were examined. Similar to previous studies, these neurons demonstrated convergent excitatory cutaneous receptive fields that were either restricted to the perineal area or extended to include the caudal half of the body (for examples, see fig. 1). Eight neurons were used in initial dose-finding experiments. Twenty neurons were studied using the full intravenous drug protocol: 10 of

Table 1. Characteristics of Studied Neurons

Neuronal Type (n)	Cutaneous RF (2:3)*	Baseline Spontaneous Activity (Hz)†	Baseline Evoked Activity (cts)‡
Abrupt (15)	12:3	14 ± 14	640 ± 315
Sustained (13)	6:7	19 ± 15	662 ± 415

Data are presented as mean ± SD.

* Number of units with convergent excitatory cutaneous receptive of the Class 2 (excited by both noxious and nonnoxious stimuli) or Class 3 (excited only by noxious stimuli) types.

† Measured before any drug administration.

‡ Difference between the total number of action potentials during the colorectal distension period (20 s, 80 mmHg) and the calculated spontaneous activity for the same period measured as counts (cts).

these neurons were classified as abrupt neurons, and 10 were classified as sustained neurons using published criteria.¹⁷ The spontaneous activity of all of the abrupt neurons was inhibited $\geq 20\%$ by the application of a noxious mechanical stimulus to a distant site (tail or forepaw). Spontaneous activity of the sustained neurons studied was not reliably inhibited as a group by tail/forepaw pinch. A summary of the characteristics of the neurons is given in table 1.

Effect of Lidocaine on Neuronal Responses

Lidocaine produced statistically significant, dose-dependent inhibition of the spontaneous and evoked activities of both sustained and abrupt neurons (see fig. 2 for individual example and fig. 3 for grouped data). The effect of intravenous lidocaine on the mean evoked activity of the sustained neurons was statistically greater than its effect on abrupt neurons ($P < 0.01$ for difference between groups on repeated measures.) Effects on the mean total activity and mean evoked activity were significantly different from baseline for the sustained neurons at all doses tested, but only significant for abrupt neurons at the highest dose tested. Effects of intravenous lidocaine on the mean spontaneous activity of abrupt and sustained neurons were qualitatively and temporally similar for both neuron types, but with quantitatively greater effects on sustained neurons.

Effect of Lidocaine on Reflex Responses

Intravenous lidocaine produced a statistically significant, dose-dependent inhibition of cardiovascular responses to CRD (change in heart rate/blood pressure; figs. 4A and 4B). Effects were transient but statistically significant at all doses. Effects of intravenous lidocaine on visceromotor responses to CRD (abdominal/hind

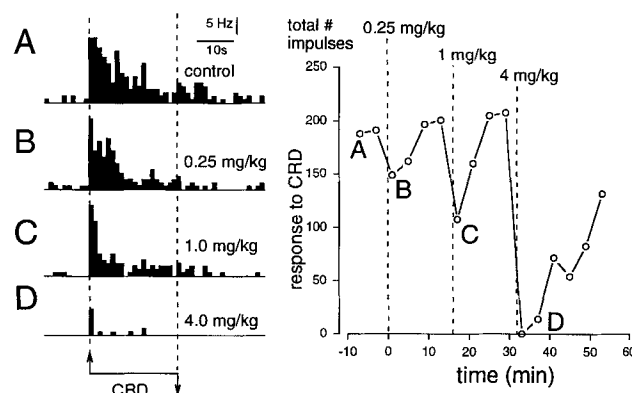


Fig. 2. Typical example of neuronal inhibition produced by intravenous lidocaine. (Right) Neuronal activity quantified as the total number of impulses (action potentials) during the period of colorectal distension (CRD; 80 mmHg, 20 s). Time zero indicates the time of first drug dosing; drug amounts are listed above and times of administration indicated by dotted lines. (Left) Peristimulus-time histograms, labeled A–D, correspond to neuronal activity indicated by the corresponding letter on the graph.

limb contractions; fig. 4C) were less robust and statistically significant only at the highest dose.

Discussion

The most significant finding of the present study was that the sodium channel blocker lidocaine produced inhibition of neuronal and reflex responses to CRD, supporting the possible utility of such agents in the treatment of visceral pain disorders. Apart from intraoperative use as a general anesthetic, intravenous lidocaine has been administered predominantly for the treatment of neuropathic pain,^{1,3–6,22,23} although effects on numerous other disorders such as myofascial pain,² burn-related pain,²⁴ headaches,²⁵ and postoperative pain²⁶ have been noted. Reports of the effectiveness of intravenous lidocaine as an analgesic have been varied, possibly because of the sharply defined dose-response relation of the drug to its analgesic effect. Ferrante *et al.*²³ noted an almost “quantal” effect of lidocaine on neuropathic pain. The drug had little effect until a particular blood level was exceeded, at which time it had an almost total inhibitory effect. If their findings can be extrapolated to other pain states, then it would be expected that studies using low doses of lidocaine might observe only a minimal effect of lidocaine, whereas studies using higher doses above a critical level would be expected to have a large effect of lidocaine.

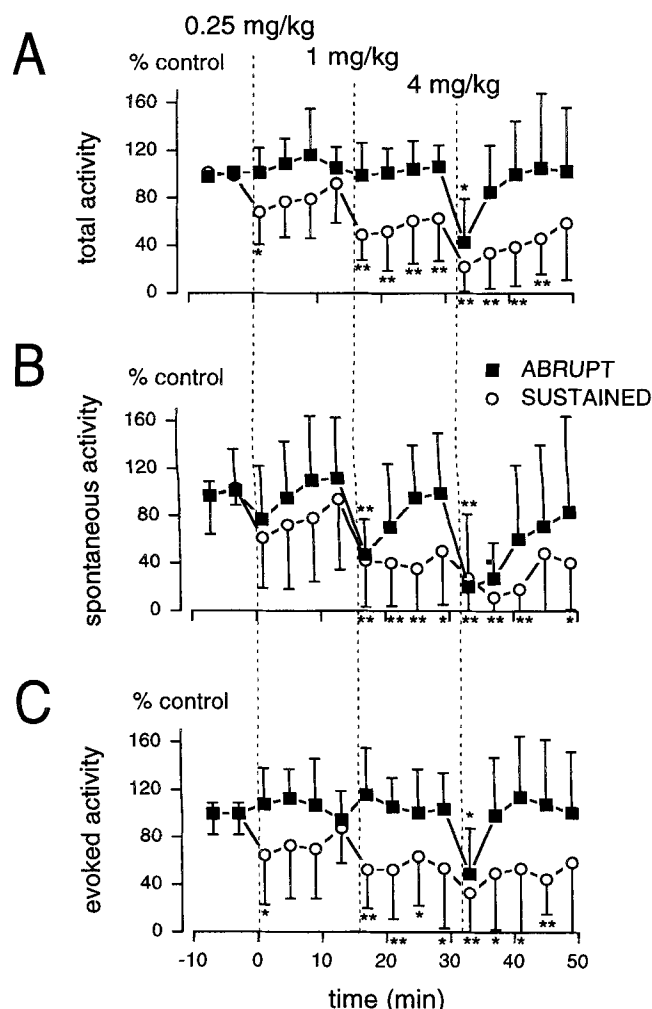


Fig. 3. Graphical demonstration of the effects of intravenous lidocaine on the mean neuronal activity of 10 sustained (open circles) and 10 abrupt (filled squares) neurons. (A) Neuronal activity is quantified as the total number of impulses during the period of colorectal distension (CRD; 80 mmHg, 20 s). (B) Neuronal activity is quantified as the spontaneous activity in the 10-s period before the onset of CRD. (C) Neuronal activity is expressed as "evoked" activity, calculated as the total activity minus the ongoing spontaneous activity. All data were normalized as a percentage of the average of the two baseline responses measured before the administration of lidocaine. Bars indicate SD. Times and doses of lidocaine are indicated above and by dotted lines. * $P < 0.05$ and ** $P < 0.01$, indicating significant reductions in activity from baseline levels of activity.

Reports of the effects of intravenously administered local anesthetics in the treatment of visceral pains have been virtually nonexistent. Bonica²⁷ noted that intravenous local anesthetics may have benefit in numerous disorders, including peptic ulcer disease. However, there is only one well-described report in which the use of systemic local anesthetics controlled visceral pain,¹ in

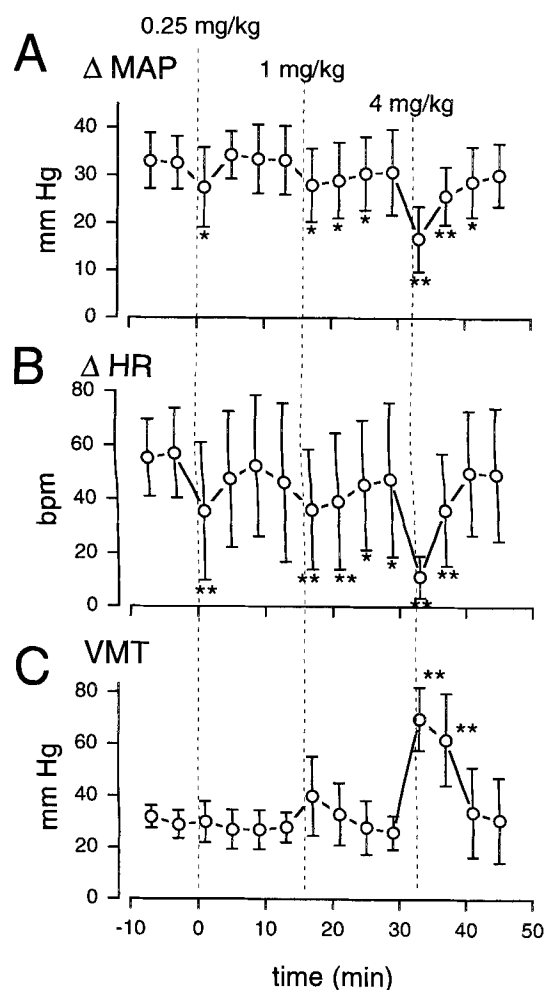


Fig. 4. Graphical demonstration of the effects of intravenous lidocaine on reflex responses to colorectal distension (CRD) in chronically instrumented, unanesthetized male rats. In eight rats, cardiovascular responses to CRD (80 mmHg, 20 s) were quantified as the change in mean arterial pressure (Δ MAP; A) and as the change in mean heart rate (Δ HR; B) during CRD in relation to the 20 s before CRD. In five rats, visceromotor reflexes were quantified as the visceromotor threshold (VMT; C), the minimal intracolonic pressure necessary to evoke an abdominal/hind limb contraction. Bars indicate SD. Times and doses of lidocaine are indicated above and by dotted lines. * $P < 0.05$ and ** $P < 0.01$, indicating significant reductions in response from baseline responses.

that case, pain arising from partial embolization of the spleen.²⁸ Favorable clinical responses to intravenous lidocaine have been reported to predict efficacy of treatment with an orally administered sodium channel blocker, mexilitine,^{4,22} but a focused search demonstrated no reports in the literature of trials of mexilitine in the treatment of visceral pain.

The precise mechanism of action of intravenous lido-

caine on pain processing has not been fully defined. At the doses used in the present study, there is little or no effect on axonal transmission in peripheral nerves,^{7,9} but profound effects within the spinal cord have been reported in single-cell, dorsal horn neuronal studies^{10,29} and in studies of evoked potentials within the spinal cord.^{7,8} Proposed spinal mechanisms include the possible involvement of neurokinin and *N*-methyl-D-aspartate-linked systems³⁰ as well as glycine-linked inhibitory systems.³¹ It has been proposed that the primary sites of action for lidocaine are within the spinal cord because the effect of intravenous lidocaine on dorsal horn neurons is longer and more potent than its effect on dorsal root ganglion neurons.³² However, actions at the level of the primary transducer are also likely. Puig and Sorkin³³ demonstrated that doses of intravenous lidocaine similar to those used in the present study (5 mg/kg) produced a transient 60% reduction in phase 2 A δ - and C-fiber activity evoked by subcutaneous formalin administration. In their study, intravenous lidocaine did not produce conduction blockade. The spontaneous activity of primary afferents arising from injured cornea,³⁴ tooth pulp,³⁵ or neuromas³⁶ is also inhibited by intravenous lidocaine. Hence, it is possible that the noted decreases in spinal neuronal activity were caused by decreased responsiveness of CRD-sensitive receptors. Future experiments of primary afferents may be able to address this possibility. Human reports of the ineffectiveness of topical lidocaine applied to the rectum at altering distension-evoked sensations³⁷ argue that the CRD-sensitive receptors are not highly lidocaine-sensitive.

To our knowledge, this is the first report of the effects of intravenous lidocaine on visceral nociceptive processing. A notable finding of this study was the differential action of lidocaine on a subgroup of spinal neurons, the sustained neurons. We have previously noted selective effects of morphine²⁰ and κ opioid receptor agonists²¹ on this subgroup when compared with the other main subgroup, abrupt neurons. We have proposed that visceral nociceptive transmission is caused by the combined activity of these two neuronal populations. The demonstration of similar dose-duration effects of lidocaine on reflex responses to CRD support that the noted neuronal responses are representative of visceral nociceptive processing. Specific differences in dose-related effects (*i.e.*, higher doses needed to affect the visceromotor response) are likely caused by differences in the effects of lidocaine on threshold phenomena *versus* suprathreshold phenomena. It is possible that differences could be caused by selective effects on the different

neuronal subclasses (*i.e.*, the inhibition of the visceromotor reflex may be secondary to the inhibition of abrupt neurons), but this implies a greater understanding of existent spinal circuitry than currently exists. Other investigators have noted effects of intravenous lidocaine on behavioral responses in neuropathic pain models³⁸⁻⁴⁰ and in the formalin test⁴⁰ using doses similar to those used in the present study.

In summary, the present study demonstrated that intravenous lidocaine produced significant dose-dependent inhibition of neuronal and reflex responses to colonic distension. This suggests potential clinical utility of sodium channel blockers in the treatment of visceral pain. The differential effect of lidocaine on two different subgroups of neurons excited by CRD further supports the assertion that visceral pain is processed through a dual pathway and presents the possibility that lidocaine could be used to define differential functions of these subgroups.

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