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Reversal of visceral and somatic hypersensitivity in a subset of hypersensitive rats by intracolonic lidocaine

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Abstract

Chronic abdominal pain is a common gastrointestinal symptom experienced by patients. We have previously shown that IBS patients with visceral hypersensitivity also have evidence of thermal hypersensitivity of the hand and foot that is reversed by rectal lidocaine jelly. We have also recently developed an animal model of chronic visceral and somatic hypersensitivity in rats treated with intracolonic trinitrobenzene sulfonic acid (TNBS). The objective of the current study was to determine the effects of intracolonic lidocaine on visceral/somatic hypersensitivity in TNBS-treated rats. A total of 20 hypersensitive rats received either 20 mg intracolonic lidocaine ($n = 10$) or saline jelly ($n = 10$). In comparison to saline jelly, intracolonic lidocaine jelly reduced responses to nociceptive visceral/somatic stimuli in hypersensitive rats. The effects were present within 5–30 min after administration of lidocaine and lasted for 6 h. Lidocaine had no effects on recovered rats or control rats that had originally been treated with intracolonic saline instead of TNBS. Local anesthetic blockade of peripheral impulse input from the colon reduces both visceral and somatic hypersensitivity in TNBS-treated rats, similar to results in IBS patients. The results provide further evidence that visceral and secondary somatic hypersensitivity in a subset of TNBS-treated rats reflect central sensitization mechanisms maintained by tonic impulse input from the colon. This study evaluates the reversal of visceral/somatic hypersensitivity in a subset of TNBS-treated rats with intracolonic lidocaine. This animal model may be used in the future to study the mechanisms of local anesthetic agents applied to the gut to reduce visceral pain.

Keywords

Irritable bowel syndrome; Lidocaine; Visceral and somatic hypersensitivity; Visceral pain; Animal model; TNBS colitis

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1. Introduction

Chronic abdominal pain is a common gastrointestinal symptom that affects large numbers of patients in the US. Even though the pathophysiology of visceral pain or functional bowel disorders is unclear, visceral hypersensitivity is a common biological marker of many functional bowel disorders such as the irritable bowel syndrome [21,29]. The cause of visceral hypersensitivity is unknown, but several mechanisms have been proposed that include triggering events such as inflammation, psychological or environmental stress, or post-injury sensitization [16,18].

Many patients with functional abdominal pain frequently complain of pain in body regions somatotopically distinct from the gut. This suggests that central hyperalgesic mechanisms may be involved and that the hypersensitivity may not be limited to the gut. Interestingly, several studies have shown that IBS patients also demonstrate hypersensitivity to nociceptive stimuli applied to somatic tissues [5,9,29,30]. These results suggest that visceral and somatic nociceptive processing overlap (viscerosomatic convergence), particularly in the lumbo-sacral distribution. Thus, tonic input from the gut may sensitize spinal cord neurons that have viscerosomatic convergence and exhibit somatotopic overlap with the gut.

Our recent study has found long-term visceral and somatic hypersensitivity in a subset of rats (18/75 or 24%) that had been given intracolonic trinitrobenzene sulfonic acid (TNBS) [34]. In this study, behavioral changes at 16 weeks were measured by nociceptive visceral, mechanical, and thermal behavioral tests following complete resolution of colitis. The subset of rats with hypersensitivity (“hypersensitive rats”) had evidence of visceral and somatic hypersensitivity on all behavioral pain tests (visceral and somatic).

These hypersensitive rats had visceral and somatic hypersensitivity in response to nociceptive colonic distension and thermal stimulation similar to that seen in a subset of IBS patients [5, 9,29,30]. IBS patients report greater pain in response to rectal distension and thermal stimulation of the extremities in comparison to controls, thereby demonstrating both visceral hypersensitivity and secondary thermal hypersensitivity. We have hypothesized that this somatic hypersensitivity, both in IBS patients and hypersensitive rats, is most pronounced in somatic areas associated with convergence of colonic and somatic afferents onto common spinal neurons [25].

In a subsequent study of IBS patients, local anesthetic blockade of peripheral impulse from the rectum/colon reduced both visceral and secondary thermal hypersensitivity in IBS patients [31]. The current study further tested this possibility in hypersensitive rats after recovery from experimentally induced colitis [34]. We hypothesized that lidocaine would reverse visceral and somatic hypersensitivity in hypersensitive rats (previously treated with TNBS). This pattern of results would provide further support for a potential animal model of functional bowel disorders and chronic visceral pain. Such a model would open the opportunity to further explore the neural and molecular mechanisms of visceral and somatic hypersensitivity present in IBS patients.

2. Methods

2.1. Animals and experimental design

A total of 100 male adult Sprague–Dawley rats weighing 200–250 g were used. A separate set of 35 rats were also used to determine serum lidocaine levels. The rats were housed in pairs under constant temperature and humidity with 12-h light–dark cycles, and were given free access to food and water. Administration of TNBS with 50% ethanol was used to produce colonic inflammation as previously described [20,34]. Using 5–6 cm of a 24 gauge catheter,

20 mg (per rat) of TNBS (Sigma Chemical Co.) in 50% ethanol (total volume, 0.4 ml), was instilled into the lumen of the colon, 3–4 cm proximal to the anus ($n = 80$). An equivalent volume of saline was administered into the colon in control rats ($n = 20$). Rats were kept in a vertical position for 5–10 min to avoid leakage of the instilled intracolonic solutions. The rats were all held in a gentle manner to avoid any stress. Rats were monitored daily for changes in body weight, body condition, physical appearance, and behavior during the 16 week period following treatment. No adverse effects were observed in any of the rats. All procedures were approved by Ohio State University and the North Florida/South Georgia Veterans Administration Health System Institutional Animal Care & Use Committees. Somatic and visceral pain testing was performed 16 weeks following administration of TNBS or saline under blinded conditions. Four types of sensory tests (colonic distension, mechanical, thermal, tail flick) were performed during the same session. The order of the tests was randomized and counterbalanced across groups to assess stress from handling and movement. Although multiple tests were used, stress was minimized by using brief tests that measured threshold responses. Each individual rat was tested in the same order throughout with a 10 min interval in between each of the different pain stimuli. The colonic balloon was not in place during the somatic tests. It was inserted before and removed immediately following the colonic distension studies. All of the behavioral testing was done following a 12 h fast. The level 25 mmHg was used as the visceral hypersensitivity threshold based on our observations in a prior study [34]. The choice of this threshold assured that there was no or little overlap in the distributions of responses across the hypersensitive group and control group.

2.2. Visceral hypersensitivity testing

2.2.1. Colonic distension—A flat bottom holder (RSTR544, 250–500 g) (Kent Scientific Corp, Torrington, CT) plastic restrainer was used to hold the unsedated animals during colonic distension. It was large enough to allow the rats to move inside of it. Because the holder is clear plastic, we were able to monitor all abdominal movement and contractions. The abdominal contractions in response to balloon distension were clearly distinct and readily recognizable compared to normal abdominal movements.

A balloon (3 cm long, 1.5 cm max diameter) made of poly-ethylene was secured to tubing attached to an automated distension device (G&J Electronic Inc., Toronto, Canada) and used to perform colonic distension. The balloon was lubricated and placed into the rat's distal colon so that the tip of the balloon was 1 cm from the anus. The rats were allowed to acclimatize 10 min before behavior testing began. The rats were restrained in a plastic containment device and received phasic distension (0–80 mmHg in 5 mmHg ascending increments of 10 s each) of the colon until the first contraction of the testicles, tail, or abdominal musculature occurred. This threshold response was considered to reflect a behavioral index of visceral sensitivity in response to a nociceptive stimulus ("1st nociceptive response") as previously described [23, 33,34]. The colonic distensions were repeated 4 times with 5 min interstimulus intervals and the mean pressures at response threshold were recorded for each rat [34]. Rats were categorized as hypersensitive to colonic distension if the 1st nociceptive response was at a colonic distension pressure of <25 mmHg as previously reported [34].

2.3. Somatic hypersensitivity testing

The colonic balloon was not in place during testing of the thermal, mechanical, and tail flick reflex pain stimuli. It was removed immediately following the colonic distension testing done above.

2.3.1. Mechanical stimulation—Mechanical hypersensitivity was measured using an electronic Von Frey device (Dynamic Plantar Aesthesiometer; Electronic Unit/Filaments and Calibration Weights, Ugo Basile S.R.L. Biological Research Apparatus, Italy). Rats were

placed on a wire mesh floor in a plastic enclosure. A computer driven filament was then extended up through the mesh floor and exerted an increasing amount of pressure (maximum 50 g) onto the rat's hind-paw. The force in grams required for the rat to withdraw its hind-paw was defined as the mechanical pain threshold. Both hind paws were tested in each rat. The stimulus was repeated 4 times following a 5 min interstimulus interval and the mean was calculated for each rat's hind-paw [34]. Rats were categorized as hypersensitive to mechanical stimulation if a force of <18 g elicited hind-paw withdrawal as previously reported [34].

2.3.2. Thermal stimulation—A thermal stimulus was delivered using the Hargreave's technique (7371 Plantar Test. From Ugo Basile S.R.L. Biological Research Apparatus, Italy) [12]. Rats were placed in a plastic enclosure on a plexiglass surface and the heat stimulus was applied underneath the plastic chamber. The time in seconds (latency) until the rat withdrew its hind-paw was recorded for each rat. Both hind paws were tested in each rat. The stimulus was repeated 4 times following a 5 min interstimulus interval and the mean was calculated for each rat's hind-paw [34].

Rats were categorized as hypersensitive to thermal stimulation if a latency of <8 s elicited hind-paw withdrawal as previously reported [34].

2.3.3. Tail flick reflex—The tail-reflex was performed by immersing the rat's tail 6–7 cm in 50 °C water. The length of time in seconds (latency) until the rat withdrew its tail was measured. The stimulus was repeated 4 times following a 5 min interstimulus interval and the mean was calculated for each rat [34]. Rats were categorized as hypersensitive to tail flick reflex if the latency for tail-withdrawal was <3.5 s as previously reported [34].

2.4. Reversal of visceral/somatic hypersensitivity

A total of 20 TNBS-treated hypersensitive rats and 20 saline-treated rats were used for the part of the experiment. The rats were allowed to rest for 24 h following the above behavioral pain testing. The rats were then randomly assigned to receive either intracolonic lidocaine jelly or saline jelly. The animals were coded with a number so that the examiners performing the pain testing procedures were blinded to which group (hypersensitive, normal control) or agent (lidocaine jelly, saline jelly) the rats received. The lidocaine agent, consisting of 20 mg of 2% lidocaine jelly in 1.0 ml (Astra USA, Inc., Westborough, MA), was applied directly into the rat colon by using 5–6 cm of a 24 gauge catheter connected to a 3 ml syringe. The lidocaine jelly was instilled into the lumen of the colon 4 cm proximal to the anus ($n = 20$, included 10 hypersensitive rats; and 10 saline control rats). An equivalent volume of saline jelly was similarly administered into the colon of control rats ($n = 20$, 10 hypersensitive rats; 10 saline control rats).

There were four technicians performing each of the stimulus testing (rectal distension, mechanical Von Frey, Hargreaves, and tail-reflex test) and one technician administered intracolonic lidocaine or saline jelly followed by the behavioral testing. The visceral and somatic stimuli used above were applied once at 5–10, 30–35 min and four repeated times at 1, 2, 4, 6, and 8 h after administration of the intracolonic lidocaine or saline agent.

2.5. Histopathological evaluation

The rats were euthanized at the conclusion of the study and the colon was removed for histopathological study. Immediately following the conclusion of the somatic and visceral pain testing, all rats were euthanized using sodium pentobarbital (120 mg/kg, IP). Following euthanasia, 4–5 cm of the distal descending colon was removed and processed for histopathology. The tissue was fixed in formalin and processed using standard techniques for H&E staining. The severity of the lesions in the colon and mucosa was graded using a grading

system previously described [2]. The pathologist who graded the colitis was blinded to which group (hypersensitive, saline) each rat belonged to. The grades of colitis included mild (+1) infiltration of a limited number of neutrophils in the lamina propria with minimal interstitial edema; moderate (+2) infiltration of a moderate number of neutrophils in the lamina propria with moderate interstitial edema; and severe (+3) diffuse infiltration of neutrophils in the lamina propria with severe interstitial edema.

2.6. Serum lidocaine levels

A separate group of 8 TNBS-treated hypersensitive rats and 8 saline-treated rats that were not in the above experiment were used to test serum lidocaine levels at 5 and 30 min and 1, 4, and 6 h. The same lidocaine agent, consisting of 20 mg of 2% lidocaine jelly in 1.0 ml (Astra USA, Inc., Westborough, MA), was instilled into the colon as above. One milliliter of venous blood was drawn and collected in a 2 ml red top tube from 6 rats at specified time points (5 and 30 min, 1, 4, and 6 h) after lidocaine jelly administration. The blood samples were centrifuged at 4 °C for 10–15 min. The serum lidocaine levels were measured and analyzed by radioimmunoassay (Rocky Point Laboratory, Gainesville, FL).

2.7. Statistical analysis

All statistics were run using Prism Version 6. Frequency distribution was used to classify the group of TNBS rats that were hypersensitive based on the distribution of the behavioral pain testing. The two groups of rats (hypersensitive, saline) were further divided into two groups that received lidocaine or saline jelly. Repeated measures analyses of two-way ANOVA followed by Bonferroni post-tests were used to analyze effects of lidocaine or saline treatment on behavioral test data. Values are expressed as means $\pm$ standard deviation (SD).

3. Results

3.1. Baseline behavioral pain testing

Shown in Table 1 are the results of the visceral and somatic pain testing in both the hypersensitive ($n = 20$) and saline ($n = 20$) treated rats. A total of 20/80 (25%) of TNBS-treated rats exhibited both somatic and visceral hypersensitivity as previously defined. These results are similar to the previous study we had reported [34]. Saline-treated rats with normal sensitivity to behavioral pain testing were used as controls to compare to the hypersensitive group. There was no observed order effect based on which specific pain stimuli were applied first.

3.2. Reversal of visceral hypersensitivity

Lidocaine jelly produced large increases in the visceral response threshold to colonic distension at 5–10, 30–35 min and at 1, 2, 4, 6, and 8 h following colonic instillation in hypersensitive rats, indicative of a large reduction in visceral hypersensitivity (Fig. 1) ($p < 0.0001$; repeated measures two-way ANOVA). Bonferroni's post-tests revealed significant differences ($p < 0.001$) at 5–10, 30–35 min and at 1, 2, 4, and 6 h after lidocaine treatment. The difference at 8 h was not statistically significant. In contrast, saline jelly had no effect on any of the hypersensitive rats (Fig. 1).

3.3. Reversal of mechanical hypersensitivity

Lidocaine jelly produced large increases in the Von Frey filament paw withdrawal thresholds at 30–35 min and at 1, 2, 4, and 6 h in hypersensitive rats, indicative of a large reduction in mechanical hypersensitivity (Fig. 2). The overall effect was statistically significant (repeated measures analyses of two-way ANOVA, $p < 0.0001$). Bonferroni's post-tests revealed significant differences at 30–35 min, and at 1, 2, 4, and 6 h ($p < 0.001$) after lidocaine treatment

(Fig. 2). The differences at 5–10 min and 8 h were not statistically significant. In contrast, saline jelly had no effect on any of the hypersensitive rats (Fig. 2).

3.4. Reversal of thermal hypersensitivity

Lidocaine jelly produced large increases in hind-paw withdrawal latency (Hargreaves test) at 30–35 min and at 1, 2, 4, and 6 h in all the hypersensitive rats (Fig. 3). Bonferroni's post-tests indicated a large reduction in thermal hypersensitivity. The overall effect was highly statistically significant (repeated measures analyses of Two-way ANOVA $p < 0.0001$). As with the Von Frey test, differences at 5–10 min and 8 h were not statistically significant. In contrast, saline jelly had no effect on any of the hypersensitive rats (Fig. 3).

3.5. Reversal of tail flick hypersensitivity

Lidocaine jelly produced large increases in the latency to the tail-reflex withdrawal response to the 50 °C water stimulus at 30–35, 45–50 min, and at 1, 2, 4, and 6 h in hypersensitive rats, indicative of a large reduction in heat hypersensitivity (Fig. 4). The overall effect was statistically significant (two-way ANOVA, $p < 0.0001$). As with the Von Frey and Hargreaves tests, differences at 5–10 min and 8 h were not statistically significant. In contrast, saline jelly had no effect on any of the hypersensitive rats (Fig. 4).

3.6. Histopathological evaluation

The colons from all rats were examined by an independent blinded investigator. Regardless of experimental treatment, rats had no evidence of colitis at 16 weeks following administration of saline or TNBS, similar to our previous study [34]. There was no evidence of neutrophils in the lamina propria or interstitial edema.

3.7. Serum lidocaine levels

No detectable serum levels of lidocaine (<1.0 mg/L; reference range: 1.5–5.0 mg/L) were found at any time points throughout the 4 h of observation (5 and 30 min, 1 and 4 h) following intracolonic lidocaine jelly administration in any of the rats (8 hypersensitive, 8 saline control rats).

4. Discussion

The current results support our hypothesis that local anesthetic blockade of peripheral impulse input from the colon reduces both visceral and secondary somatic hypersensitivity in the subset of TNBS-treated rats (hypersensitive rats) that maintain visceral and somatic hypersensitivity long after histological recovery of TNBS-induced colitis. These findings parallel our earlier lidocaine studies in IBS patients [31,32].

Intracolonic lidocaine reduced hypersensitivity from colonic distension, Von Frey mechanical stimulation, Hargreaves thermal stimulation of the hind-paw, and tail-withdrawal responses in subset of hypersensitive rats. Lidocaine reduced the hypersensitivity to colonic distension 5–10 min after the onset of the treatment (Fig 1) and reduced both mechanical and thermal somatic hypersensitivity 30–35 min after lidocaine treatment (Figs. 2–4). Both visceral and somatic hypersensitivity were decreased for 6 h. The rapid onset of lidocaine's action (5 min) linked with the absence of detectable blood levels of lidocaine (<1.0 mg/L; reference range: 1.5–5.0 mg/L) throughout the 8 h of observation, suggests that the analgesic effects of lidocaine were the result of local anesthesia, not systemic absorption of lidocaine. That lidocaine attenuated the somatic and visceral hypersensitivity further supports the role of tonically active colonic afferents that induce central sensitization. It is not surprising that even after 16 weeks of tonic afferent input from the colon that lidocaine was able to cause a rapid reversal of the hyperalgesia

(i.e., 5 min after administration). Some conditions of central sensitization are dynamically maintained by tonic input from the periphery. When this input is blocked by local anesthesia, the central sensitization is reduced or eliminated. This rapid reversal of chronic hyperalgesia has also been shown with intracutaneous lidocaine injections in CRPS patients [11] and in IBS patients with intrarectal lidocaine [31,32]. Another example is following sciatic nerve ligation [14]. In this CCI rat model, the hypersensitivity is reduced when the sciatic nerve is locally anesthetized [17].

Rats with chronic pain conditions and patients with fibromyalgia or IBS often display widespread body zones of thermal, mechanical, and deep tissue hypersensitivity [28,29]. Since anesthetic nerve blocks reverse both primary and secondary hypersensitivity in animal and human studies of neuropathic, fibromyalgia, and IBS pain, it is possible that widespread central sensitization and consequent secondary hyperalgesia is maintained by tonic impulse input from damaged or dysfunctional primary nociceptive afferent neurons [10,11,17,24]. The results of this current study further support this possibility, further validating an animal model of chronic visceral and somatic hypersensitivity.

However, the literature on somatic hypersensitivity in IBS is somewhat contradictory and we have previously suggested the hypothesis that if somatic hypersensitivity reflects N-methyl-D-aspartate (NMDA) receptor mechanisms, hypersensitivity would be more evident using long duration heat tests than using brief duration tests [25]. The latter are more unlikely to activate NMDA receptors. Whereas 20-s nociceptive heat stimulation is very likely to tonically activate C-nociceptive afferents and NMDA receptor mechanisms, brief mechanical stimulation is less likely to activate NMDA receptor mechanisms for any significant length of time [6,29,30]. There are other possible explanations as well. For example, IBS patients may be very heterogeneous with regard to the severity of their condition and those with both somatic and visceral hypersensitivity may reflect a more advanced condition. The presence or absence of somatic hypersensitivity may also relate to diverse etiologies of IBS. This possibility is suggested by animal studies in which neonatal maternal separation predisposes adult Long-Evans rats to develop visceral hypersensitivity, reduced somatic analgesia, and increased colonic motility [7]. The stress-induced cutaneous analgesia was significantly less in the maternal separation rats and suggests a compromised ability of the rats to activate endogenous opioidergic pain inhibitory systems [7].

Lidocaine is an analgesic agent that can be selectively used to induce local analgesia, or can be administered systemically to produce central analgesic effects. Systematic administration of lidocaine has been shown to produce analgesia in a variety of neuropathic pain states in human studies and to reduce the intensity and extent of associated allodynia at doses that do not produce symptoms of system toxicity [3,4,13,15]. Abram and Yaksh also reported that systemic lidocaine blocks nerve injury-induced hyperalgesia and nociceptor-driven spinal sensitization in the rats [1]. The exact mechanism by which lidocaine improves pain in such conditions is not yet clear. Intravenous lidocaine has also been shown to block the visceromotor response to colorectal distension in decerebrate male rats [22]. Possible mechanisms of action includes effects on central nervous system processing of pain or on impulse conduction in injured nerves by blocking sodium and/or calcium gated channels. Lidocaine may also attenuate the affects of colitis on the intrinsic and/or extrinsic nerves by reducing mast cell hyperplasia and exerting anti-inflammatory effects [19].

The present study shows that the duration of lidocaine's effect extends at least 6 h, well beyond the expected 3-h effect of lidocaine. Extended intrarectal effects of lidocaine were also observed for ongoing pain in IBS patients [32]. Extended durations of lidocaine effects also have been observed in human patients with complex regional pain syndrome (CRPS) and in animal models of CRPS [17,24]. Local anesthetic effects are known to have long duration

normalizing effects on abnormal sodium and calcium channels [8]. In further support of this possibility, we recently found upregulation of NMDA receptors in both the spinal cord and colon of hypersensitive rats (paper in preparation). These receptors depend on calcium channels that are known to be blocked by local anesthetics [27].

Our current results extend the mechanisms of lidocaine analgesia by demonstrating that local anesthesia of the colon reverses visceral and somatic hypersensitivity in hypersensitive rats, similar to effects seen in human IBS patients. The data also shows that saline jelly has no effects on colonic hypersensitivity from colonic distension in controls and hypersensitive rats, consistent with Sabate et al. and our early human study [26,31]. From a therapeutic perspective, it is encouraging that lidocaine had selective effects on visceral and somatic hypersensitivity without eliminating all rectal sensitivity and without producing significant serum levels of lidocaine [31,32]. The reversal of hypersensitivity in absence of significant serum levels of lidocaine suggests that colonic administration of lidocaine jelly may block tonic impulse input from the colon that would otherwise maintain central sensitization and neuronal hyperexcitability. These effects offer the opportunity to conduct molecular and neuropharmacological studies of this debilitating and painful condition.

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Fig. 1.

Bar graph of colon distension pressures in mmHg vs. time course in hypersensitive rats following lidocaine jelly or saline jelly treatment. White bars indicate mean responses in 10 hypersensitive rats that received saline jelly treatment; black bars indicate mean responses of 10 hypersensitive rats that received lidocaine jelly treatment. Error bars are expressed as means $\pm$ standard deviation.

Fig. 2.

Bar graph of mechanical threshold testing on hind paws in force/g vs. time course in hypersensitive rats following lidocaine jelly or saline jelly treatment. White bars indicate mean responses of 10 hypersensitive rats that received saline jelly treatment; black bars indicate mean responses of 10 hypersensitive rats that received lidocaine jelly treatment. Error bars are expressed as means $\pm$ standard deviation.

Fig. 3.

Bar graph of thermal sensitivity testing on hind paws shown as latency (s) vs. time course in hypersensitive rats following lidocaine jelly or saline jelly treatment. White bars indicate mean responses of 10 hypersensitive rats that received saline jelly treatment; black bars indicate mean responses of 10 hypersensitive rats that received lidocaine jelly treatment. Error bars are expressed as means $\pm$ standard deviation.

Fig. 4.

Bar graph of tail flick shown as latency (s) vs. time course following lidocaine jelly or saline jelly treatment. White bars indicate mean responses of 10 hypersensitive rats that received saline jelly treatment; black bars indicate mean responses of 10 hypersensitive rats that received lidocaine jelly treatment. Error bars are expressed as means $\pm$ standard deviation.

Table 1

Results of behavioral visceral and somatic hypersensitivity testing

Behavior tests	Saline control rats (n = 20)	Hypersensitive rats (n = 20 of 100)	Recovered rats (n = 80 of 100)	One-way ANOVA
Colonic distention (mmHg)	52.35 ± 10.16	17.40 ± 4.88	54.56 ± 9.01	p < 0.001
Mechanical stimuli (force/g)	31.68 ± 7.07	10.20 ± 5.31	31.88 ± 6.84	p < 0.001
Thermal stimuli (latency/s)	15.83 ± 4.11	5.05 ± 1.68	16.22 ± 3.32	p < 0.001
Tail flick reflex (latency/s)	5.96 ± 1.28	2.53 ± 0.84	6.24 ± 1.21	p < 0.001

All values represent means ± standard deviation (SD).