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Differential effects of amitriptyline on perception of somatic and visceral stimulation in healthy humans

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Gorelick, Adam B., Sherin S. Koshy, Forrest G. Hooper, Todd C. Bennett, William D. Chey, and William L. Hasler. Differential effects of amitriptyline on perception of somatic and visceral stimulation in healthy humans. *Am. J. Physiol.* 275 (*Gastrointest. Liver Physiol.* 38): G460–G466, 1998.—Tricyclic antidepressants treat chronic pain both in patients with somatic illness and with functional bowel disorders. We compared the effects of amitriptyline on perception of cutaneous and gastrointestinal stimulation to assess differential analgesic effects of tricyclics on somatic and visceral pain. Cutaneous electrical stimulation and rectal and esophageal distension were performed before and after 21 days of double-blind 50 mg amitriptyline vs. placebo in healthy volunteers. Amitriptyline increased currents that elicited cutaneous threshold, moderate discomfort, and moderate pain compared with basal ($P < 0.05$), whereas placebo had no effect. Amitriptyline had no effect on perception of rectal and esophageal distension and did not alter luminal compliance; thus the lack of effect on perception is not due to altered visceral elastic wall properties. In conclusion, amitriptyline reduces perception of cutaneous stimulation but does not alter visceral perception or compliance. This investigation demonstrates differential effects of tricyclics on somatic and visceral afferent function in healthy humans and provides insight into mechanisms of action in chronic pain both from somatic disease and from functional bowel disorders.

gastrointestinal motility; luminal distension; functional colonic disorders; irritable bowel syndrome; chest pain

TRICYCLIC ANTIDEPRESSANT agents have proven to be effective at symptom control in a variety of chronic pain syndromes. In placebo-controlled studies such drugs reduce pain in many somatic pain syndromes, including diabetic neuropathy, postherpetic neuralgia, tension headaches, and fibromyalgia (18). Recent investigations further document the efficacy of antidepressant agents in pain reduction in functional bowel disorders, including irritable bowel syndrome (IBS) and noncardiac chest pain (NCCP), indicating that this class of drugs may be useful in conditions of chronic visceral pain as well as pain from somatic sites (4, 5, 23, 35).

The mechanisms of action of tricyclic antidepressant agents in chronic pain syndromes are poorly understood. Perception of somatic stimulation is mediated by well-myelinated peripheral afferent nerves (26). Thus somatic afferent activation such as with thermal, mechanical, or electrical stimuli is perceived as a well-localized and easily characterized sensation. Tricyclics reduce pain perception in experimental models of somatic pain production (24). In contrast, perception of noxious gastrointestinal stimuli, such as with luminal

distension, involves activation of unmyelinated or poorly myelinated peripheral visceral afferent fibers (32). As a consequence, visceral pain is poorly localizable and difficult to characterize by the subject (4). It is unknown whether tricyclic antidepressants have similar inhibitory effects on perception of experimental visceral pain.

The aim of this investigation was to determine if amitriptyline, administered for 21 days in a placebo-controlled, double-blind fashion to healthy volunteers, has differential inhibitory effects on perception of innocuous and painful somatic and visceral stimuli. Amitriptyline was given at a dose that has been demonstrated to reduce symptoms in patients with chronic pain (5, 13, 20). The somatic stimulus was a train of cutaneous electrical pulses, whereas stimulation of visceral afferent fibers was provided by intermittent, isobaric phasic distension of the rectum and esophagus. Similar techniques have been demonstrated to elicit visceral pain in healthy volunteers as well as IBS and NCCP patients (29, 38). Through these investigations, we hoped to gain insight into the differential actions of tricyclic antidepressant agents in chronic somatic and visceral pain syndromes.

MATERIALS AND METHODS

Subject Population

Fourteen healthy volunteers (7 men and 7 women, 19–52 yr old), participated in the study after approval by the University of Michigan Institutional Review Board for Human Subject Research. None of the subjects was taking medications known to alter perception or gastrointestinal motility, and none had previous gastrointestinal surgery, underlying diseases altering perception, active cardiopulmonary disease requiring specialized monitoring, a history of cardiac arrhythmias, or a known intolerance to amitriptyline therapy. Written informed consent was obtained from all study subjects before participation.

Study Protocol

All subjects underwent baseline testing of cutaneous and visceral perception as will be described. Subjects were then randomized to 50 mg amitriptyline (Elavil, Stuart Pharmaceuticals, Wilmington, DE) vs. a placebo identical in appearance. This randomization was blinded to investigators and arranged by the Investigational Drug Service at the University of Michigan Medical Center. Subjects were given 28 pills and were instructed to take one pill each day at bedtime. At the completion of 21 days, subjects returned to repeat the cutaneous and visceral perception studies. Pill counts were performed at the time of these follow-up studies to ensure compliance with the medications.

Cutaneous Perception Studies

Perception of nonnoxious and painful cutaneous stimulation was tested before and after randomization to amitriptyline or placebo. The stimulus involved electrical stimulation of the forearm using a Transcutaneous Electrical Nerve Stimulator (Medtronic Nortech, San Diego, CA), which provides an oscillating biphasic electrical current of varying intensity (125 Hz frequency, 100 μ s pulse width). Electrode patches were placed 10 cm apart on the ventral surface of the dominant forearm. When necessary, the skin was shaved and gently abraded to achieve good electrical contact. Current was delivered in ascending ramp-like fashion from 0 to 65 mA at 30 mA/min. The levels of stimulation required to introduce threshold perception, moderate discomfort, and moderate pain were assessed. Each stimulation was repeated twice at 15-min intervals, and the results for each volunteer represented the mean response of the two stimulations.

Visceral Perception Studies

Perception of nonnoxious and painful rectal and esophageal distension was tested before and after randomization to amitriptyline or placebo. All studies of visceral perception were performed after overnight fasting on the same day \sim 1 h after completion of cutaneous perception testing.

Rectal perception. Rectal perception experiments were performed first. For these studies, a highly compliant polyethylene rectal bag with a length of 11 cm and a maximum volume of 500 ml was sutured to an 18-Fr polyvinyl catheter proximally and distally to ensure radial but not longitudinal inflation. After administration of a 1,000-ml warm tap water enema to evacuate the rectum, the deflated polyethylene bag was introduced into the rectum. The catheter was connected to an electronic barostat (Isobar-3; G&J Electronics, Ontario, Canada) to measure changes in rectal tone. Inflation of the bag was controlled by a single 700-ml cylinder within the barostat. Pressures were recorded within the cylinder apparatus. After an equilibration period of 20 min but before inflation of the rectal bag, volunteers were instructed to report when they experienced sensations of threshold perception, moderate discomfort, and moderate pain. The volunteer was placed in the left lateral decubitus position with knees flexed and asked not to change position for the duration of the rectal distension study. Intermittent phasic inflation of the rectal bag was performed in ascending fashion in 2-mmHg intervals from 4 mmHg to the maximally tolerated pressure with 1-min inflation periods followed by 1-min deflation periods. Volunteers were blinded to the inflation protocol, which was performed silently out of view. The inflation sequence was repeated after a 30-min period of deflation, and the rectal bag was withdrawn. There were no reproducible differences in perception between the first and second inflation sequences.

Esophageal perception. After completion of the rectal distension studies, assessment of esophageal perception was performed. For these studies, a highly compliant polyethylene bag with a length of 8 cm and a maximal volume of 250 ml was sutured to a 16-Fr polyvinyl catheter proximally and distally to ensure radial but not longitudinal inflation. To determine the location of the lower esophageal sphincter, a pH probe (Synectics Medical, Stockholm, Sweden) was orally passed into the stomach. The probe was withdrawn at a rate of 1 cm/s, and the distance at which the pH increased to >4 was recorded. The catheter with the compliant esophageal bag was passed orally after topical lidocaine spray, such that the distal aspect of the bag was 5 cm above the pH-determined lower esophageal sphincter. As with the rectal studies, the

catheter was connected to the electronic barostat, which regulated bag inflation via a single 700-ml cylinder. After an equilibration period of 20 min but before bag inflation, volunteers were instructed to report when they experienced sensations of threshold perception, moderate discomfort, and moderate pain. The volunteer was placed in a semirecumbent position at 45° and instructed not to change position for the duration of the distension study. Intermittent phasic inflation of the esophageal bag was performed in ascending fashion in 2-mmHg intervals from 4 mmHg to the maximally tolerated pressure with 1-min inflation periods followed by 1-min deflation periods. As with the rectal studies, volunteers were blinded to inflations, and inflation sequences were repeated after a 30-min deflation period. There were no reproducible differences in perception between the first and second inflation sequences.

Data analysis. Changes in intrabag pressure and volume were recorded on a paper chart recorder (model R611; Sensor-Medic, Anaheim, CA). The chart recorder was interfaced with a personal computer (4DX2-66V; Gateway 2000, North Sioux City, SD) via an analog-to-digital converter (DAS-16; Metrabyte, Taunton, MA) which digitized the analog data at a frequency of 1 Hz. Pressure and volume data were imported in spreadsheet format to commercially available software (Lotus 1-2-3, Release 2; Lotus Development, Cambridge, MA). The mean pressures and volumes which elicited reports of threshold perception, moderate discomfort, and moderate pain were calculated from the two inflation sequences for rectal and esophageal distension before and after completion of the 21-day course of amitriptyline or placebo. The slope of the linear portion of the volume-pressure curve from each inflation sequence was calculated to determine rectal and esophageal compliance. The mean compliance value was then calculated from the individual slopes of the volume-pressure curves from each of the two inflation sequences performed at each anatomic site. There were no reproducible differences in compliance between the first and second inflation sequences.

Statistical Analysis

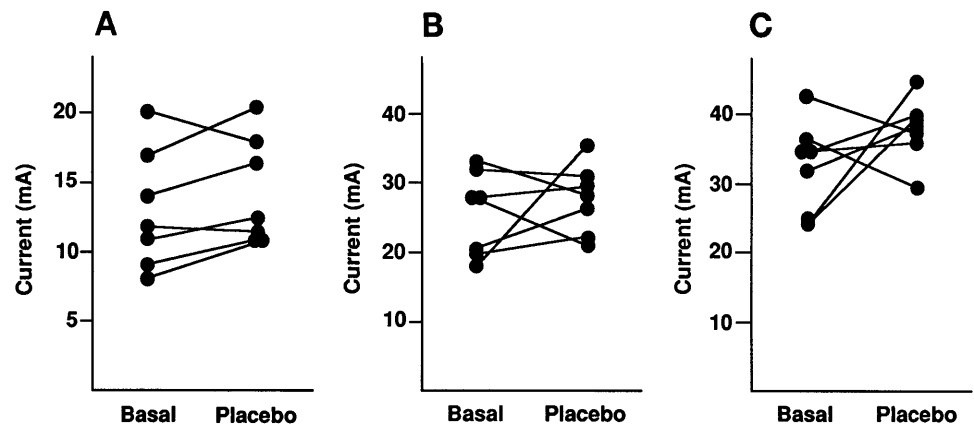
All results were expressed as means \pm SE. The cutaneous currents and intraluminal pressures which elicited the different levels of perception were compared by the two-tailed Student's *t*-test for paired observations. Similarly, the two-tailed Student's *t*-test compared rectal and esophageal compliance values. Values after amitriptyline or placebo were compared with values obtained from the basal studies; thus each volunteer served as his or her own control. Additional unpaired *t*-test analysis of posttreatment data between treatment groups was performed to confirm the results of paired *t*-testing. A *P* value of 0.05 was used to indicate statistical significance.

RESULTS

Cutaneous Perception Studies

Somatic afferent neural function was tested with cutaneous electrical stimulation before and after amitriptyline treatment in a double-blind, placebo-controlled fashion. Under basal conditions, those individuals randomized to the placebo arm reported threshold perception, moderate discomfort, and moderate pain at cutaneous currents of 13 ± 2 , 26 ± 2 , and 33 ± 2 mA, respectively (Fig. 1, A-C). After 21 days of placebo administration, currents needed to elicit these levels of perception were unchanged [14 ± 2 , 28 ± 2 , 38 ± 2 mA,

Fig. 1. Cutaneous electrical currents required to elicit threshold perception (A) and sensations of moderate discomfort (B) and moderate pain (C) are shown for those individuals randomized to placebo arm. Twenty-one days of placebo did not modify currents needed to elicit these levels of cutaneous perception ($n = 7$).



all $P =$ not significant (NS); Fig. 1, A-C]. Under basal conditions, those volunteers randomized to the amitriptyline arm reported threshold perception, moderate discomfort, and moderate pain at cutaneous currents of 13 ± 1 , 22 ± 2 , and 30 ± 2 mA, respectively (Fig. 2, A-C), values that were not different from those of the placebo group ($P =$ NS). After 21 days of amitriptyline treatment, volunteers reported threshold perception at the significantly greater current of 20 ± 3 mA (Fig. 2A; $P < 0.05$ vs. basal values for the amitriptyline group and vs. posttreatment values for the placebo group). On further administration of cutaneous current to the maximum of 65 mA, only three volunteers reported moderate discomfort and two volunteers experienced moderate pain (Fig. 2, B and C; $P < 0.05$ vs. basal values for the amitriptyline group and vs. posttreatment values for the placebo group). The other individuals reported sensations ranging from mild discomfort to mild pain (in 1 volunteer), indicating that only currents in excess of the maximum delivered by the electrical stimulator would be expected to induce more intense sensations in these individuals.

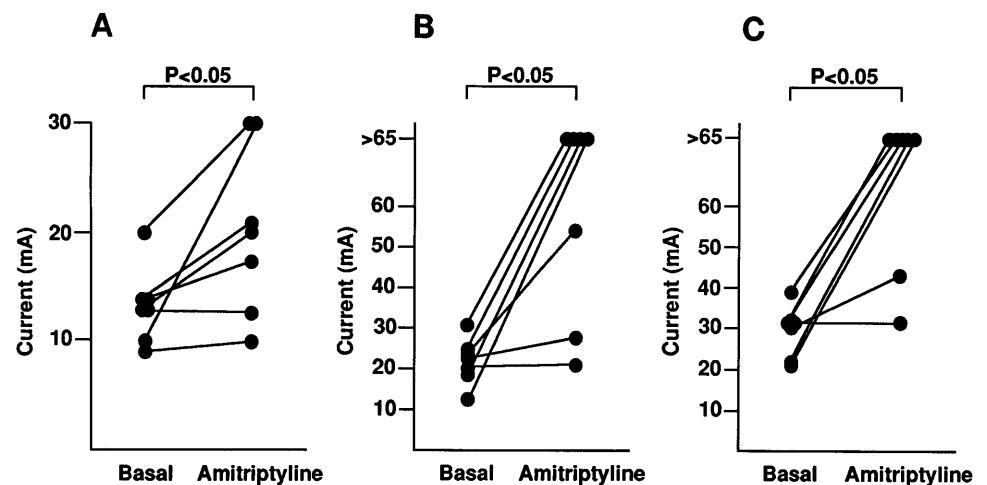
Visceral Perception Studies

Intermittent phasic rectal and esophageal distension was performed before and after 21 days of amitriptyline treatment in double-blind, placebo-controlled fashion

in the same healthy volunteers to compare the effects of amitriptyline on somatic and visceral afferent neural function.

Rectal perception. Under basal conditions those individuals in the placebo arm experienced threshold perception, moderate discomfort, and moderate pain with isobaric rectal distension at pressures of 11 ± 1 , 28 ± 2 , and 34 ± 3 mmHg, respectively (Fig. 3A). After 21 days of placebo administration, the rectal pressures required to elicit these levels of perception were unchanged compared with basal values (14 ± 2 , 31 ± 4 , and 36 ± 4 mmHg, all $P =$ NS; Fig. 3A). Similarly, there was no effect of placebo on the maximally tolerated rectal balloon volume (basal 208 ± 32 , placebo 267 ± 37 ml, $P =$ NS). Under basal conditions, those volunteers randomized to the amitriptyline arm reported threshold perception, moderate discomfort, and moderate pain at rectal pressures of 12 ± 2 , 26 ± 3 , and 33 ± 3 mmHg, respectively (Fig. 3B), values that were not different from the placebo group ($P =$ NS). After 21 days of amitriptyline treatment, the rectal pressures required to elicit these sensations were unchanged (13 ± 2 , 30 ± 4 , 36 ± 4 mmHg, all $P =$ NS; Fig. 3B). As with placebo, amitriptyline administration had no effect on the maximally tolerated rectal balloon volume (basal 221 ± 28 ml, amitriptyline 232 ± 33 ml, $P =$ NS).

Fig. 2. Cutaneous electrical currents required to elicit threshold perception (A) and sensations of moderate discomfort (B) and moderate pain (C) are shown for those individuals randomized to amitriptyline arm. Twenty-one days of amitriptyline treatment produced significant increases in cutaneous currents needed to elicit these levels of cutaneous perception compared with basal levels (all $P < 0.05$, $n = 7$).



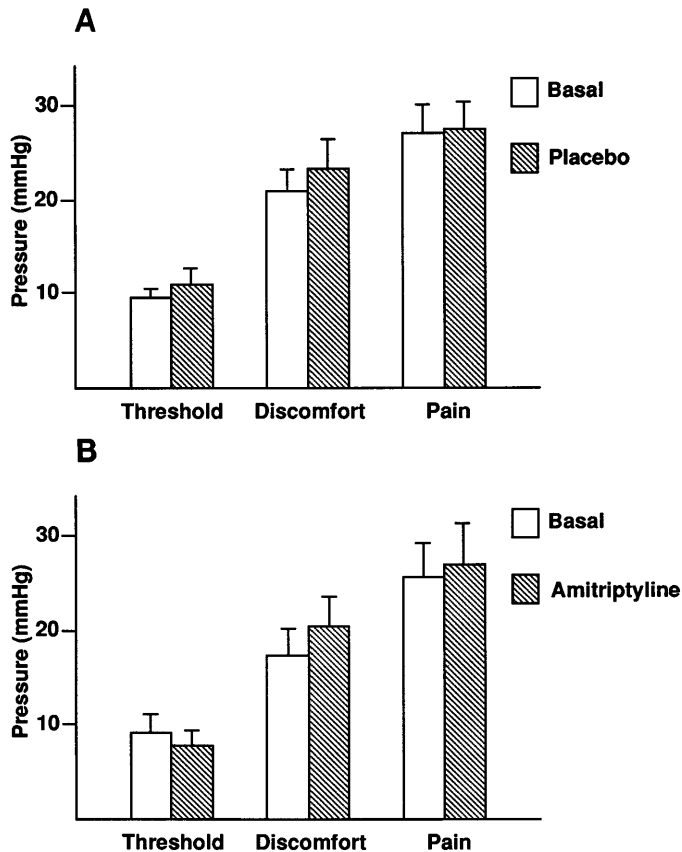


Fig. 3. Pressures generated by intermittent phasic distension of rectum that were required to elicit threshold perception and sensations of moderate discomfort and pain are shown for individuals in the placebo (A) and amitriptyline (B) arms. Neither placebo nor amitriptyline blunted perception of rectal distension at any intraluminal pressure tested. All results are means \pm SE; $n = 7$ for each arm.

Esophageal perception. Under basal conditions those individuals randomized to the placebo arm experienced threshold perception, moderate discomfort, and moderate pain during isobaric esophageal distension 5 cm above the lower esophageal sphincter at pressures of 10 ± 1 , 21 ± 2 , and 27 ± 3 mmHg, respectively (Fig. 4A). After 21 days of placebo administration, esophageal pressures required to elicit these levels of perception were not different from basal values (11 ± 1 , 23 ± 3 , and 28 ± 3 mmHg, all $P = \text{NS}$; Fig. 4A). Similarly, there was no effect of placebo on maximally tolerated esophageal balloon volumes (basal 97 ± 12 ml, placebo 118 ± 22 ml, $P = \text{NS}$). Under basal conditions, those volunteers randomized to the amitriptyline arm reported threshold perception, moderate discomfort, and moderate pain at esophageal pressures of 9 ± 2 , 17 ± 3 , and 26 ± 3 mmHg, respectively (Fig. 4B), values that were not different from those of the placebo group ($P = \text{NS}$). After 21 days of amitriptyline treatment, the esophageal pressures required to elicit these sensations were unchanged (8 ± 2 , 20 ± 3 , and 28 ± 4 mmHg, all $P = \text{NS}$; Fig. 4B). As with placebo, amitriptyline had no effect on the maximally tolerated esophageal balloon volume (basal 94 ± 17 ml, amitriptyline 102 ± 26 ml, $P = \text{NS}$).

Table 1. Effects of amitriptyline on visceral compliance

Stimulus Site	Compliance, ml/mmHg			P Value
	Treatment Group	Basal	Posttreatment	
Rectum	Placebo	7.8 ± 0.8	8.6 ± 1.1	NS
	Amitriptyline	8.0 ± 0.7	7.7 ± 0.8	NS
Esophagus	Placebo	3.8 ± 0.8	4.2 ± 0.7	NS
	Amitriptyline	3.8 ± 0.3	3.9 ± 0.4	NS

Values are means \pm SE; $n = 7$ subjects/group. NS, not significant.

Visceral compliance. To determine if the lack of effect of amitriptyline on visceral perception results from changes in rectal and esophageal elastic wall properties, compliance values were calculated before and after amitriptyline treatment given in a double-blind, placebo-controlled fashion. Intermittent phasic rectal distension produced increasing volumes in all volunteers (Table 1). Compliance values obtained by calculating the slopes of the linear portions of the volume-pressure relationships were not different before and after placebo administration (basal 7.8 ± 0.8 , placebo 8.6 ± 1.1 ml/mmHg, $P = \text{NS}$). Similarly, rectal compliance was unaffected by amitriptyline treatment (basal 8.0 ± 0.7 , amitriptyline 7.7 ± 0.8 ml/mmHg, $P = \text{NS}$ vs. basal).

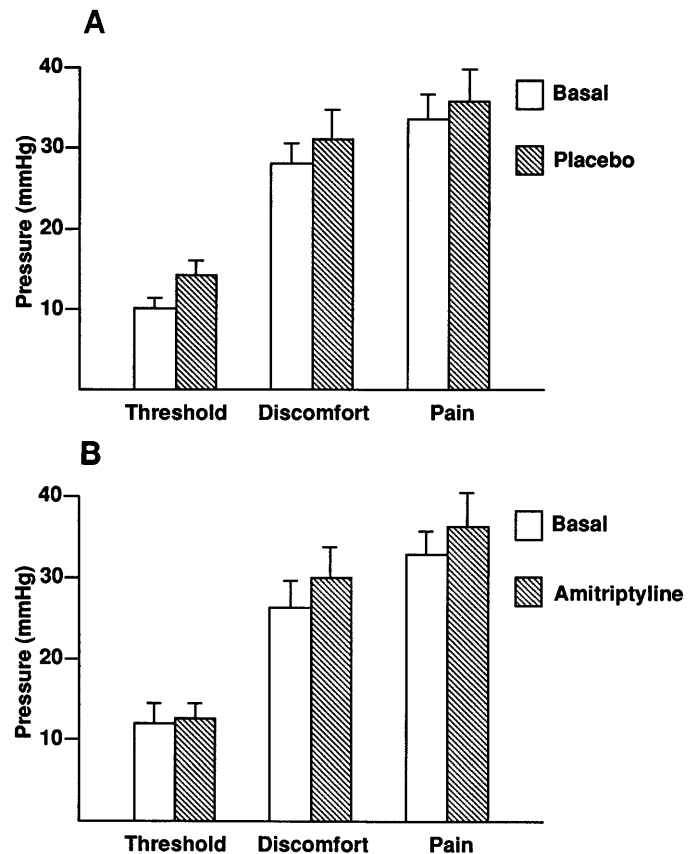


Fig. 4. Pressures generated by intermittent phasic distension of esophagus that were required to elicit threshold perception and sensations of moderate discomfort and pain are shown for individuals in the placebo (A) and amitriptyline (B) arms. Neither placebo nor amitriptyline blunted perception of esophageal distension at any intraluminal pressure tested. All results are means \pm SE; $n = 7$ for each arm.

values for the amitriptyline group and vs. posttreatment values for the placebo group).

As with rectal distension, intermittent phasic esophageal distension produced progressive increases in volume (Table 1). Compliance values were not significantly different before and after placebo administration (basal 3.8 ± 0.8 , placebo 4.2 ± 0.7 ml/mmHg, $P = \text{NS}$). Similarly, esophageal compliance was not altered by 21 days of amitriptyline treatment (basal 3.8 ± 0.3 , amitriptyline 3.9 ± 0.4 ml/mmHg, $P = \text{NS}$ vs. basal values for the amitriptyline group and vs. posttreatment values for the placebo group). These comparisons demonstrate that the lack of effect of amitriptyline on visceral perception is not due to altered visceral elastic wall properties.

DISCUSSION

Tricyclic antidepressant agents, such as amitriptyline, reduce pain in a wide range of conditions, including diabetic neuropathy, postherpetic neuralgia, headaches, arthritis, fibromyalgia, chronic back pain, cancer-associated pain, thalamic pain, facial pain, and phantom limb pain (18). The functional bowel disorders, including IBS and NCCP, are prevalent conditions of unknown etiology and uncertain pathogenesis (15). Both controlled and uncontrolled studies suggest that the antidepressant agents may have significant efficacy in these patients as well. In blinded, placebo-controlled trials, the tricyclic agents desipramine, trimipramine, nortriptyline, and amitriptyline were demonstrated to reduce abdominal pain in patients with IBS (14, 23, 30, 35). In the largest uncontrolled series to date, antidepressant agents in the tricyclic and selective serotonin reuptake inhibitor classes produced symptomatic improvement and complete symptom remission in 89% and 61% of IBS patients, respectively (5). Similarly, antidepressants reduce chest pain in patients with NCCP (4).

The mechanisms and sites of action of the analgesic effects of the tricyclic agents are incompletely characterized. Amitriptyline inhibits neural reuptake of serotonin and norepinephrine. Clinical studies of selective serotonin reuptake inhibitors in chronic pain provide contradictory results, with some studies showing analgesic efficacy and others showing no effect (19, 27). Recent investigations suggest instead that inhibition of norepinephrine uptake may be more important (7). In mouse writhing assays, amitriptyline exhibits potent analgesia when given intracerebroventricularly (34). In contrast, the serotonin reuptake inhibitors zimelidine, alaproclate, and chlorimipramine act selectively on spinal sites (12). Finally, in a study comparing disparate nociceptive stimuli, amitriptyline was shown to act on spinal sites to inhibit the withdrawal reflex to noxious electrical stimulation but was demonstrated to blunt the response to painful thermal stimulation when administered intracerebroventricularly, suggesting a central site of action (10). In healthy volunteers, a single dose of imipramine increases the pain tolerance thresholds to heat and pressure pain, demonstrating

the presence of a hypoalgesic effect in response to certain somatic stimuli in a human model (24).

There is little information about the differential effectiveness of tricyclic agents in blunting sensory responses to innocuous and painful somatic and visceral stimulation. In the present investigation, we employed well-characterized models of afferent neural activation in human subjects. Cutaneous electrical stimulation has served as a reproducible somatic stimulus both in healthy volunteers and in patients with chronic somatic pain syndromes (1, 16, 31). Somatic electrical stimuli activate predominantly well-myelinated A- δ afferent neural pathways which subserve the well-localized, easily characterized pain of somatic stimulation (1, 31, 32). Selective distension of different regions of the gastrointestinal tract has been employed to investigate the underlying pathophysiology of the functional bowel disorders, a methodology that significantly activates unmyelinated or poorly myelinated visceral afferent C-fibers that mediate the poorly localized, vague nature of abdominal pain (22, 29, 32, 36, 38). Recent investigations suggest that IBS and NCCP patients have enhanced perception of distension activation of visceral afferent pathways and associated changes in referral patterns for abdominal and chest pain without alterations in visceral compliance (22, 29, 36, 38). A current area of research centers on medications that blunt this visceral hyperalgesia. To date, medication classes that have been shown to blunt perception of rectal, colonic, gastric, or esophageal distension in healthy volunteers and patients with functional bowel disorders include serotonin 5-HT₃ receptor antagonists, the somatostatin analog octreotide, and the κ -opioid agonist fedotozine (6, 9, 16, 17, 25). Furthermore, recent investigations have revealed significant clinical efficacy of 5-HT₃ receptor antagonists and κ -opioid agonists in patients with IBS and functional dyspepsia, indicating an emerging role for visceral analgesic agents in functional gastrointestinal disorders (2, 8, 28).

The aim of the present study was to compare the effects of amitriptyline on perception of cutaneous stimulation with perception of gastrointestinal luminal distension in healthy volunteers. This investigation demonstrated that amitriptyline blunts perception of innocuous and noxious cutaneous electrical stimulation, suggestive of inhibition of somatic afferent neural function. In contrast, amitriptyline did not affect perception of nonpainful and painful rectal and esophageal distension and had no effect on visceral compliance, indicating that the tricyclic agent has no inhibitory effects on visceral afferent function mediating perception of distension. This investigation has potentially important implications for the use of tricyclic antidepressants in the treatment of chronic somatic pain syndromes and functional bowel disorders. The demonstration that amitriptyline blunts perception of cutaneous electrical stimulation in healthy humans indicates that the presence of preexisting pain is not necessary for the tricyclics to exhibit analgesia to somatic stimulation. The anatomic site of action of the inhibitory effect

of amitriptyline in response to this somatic stimulus is unknown.

Given the efficacy of tricyclic antidepressants in the treatment of functional bowel disorders, it is more difficult to explain the inability of amitriptyline to blunt perception of rectal and esophageal distension. In contrast to somatic pain, it is conceivable that visceral hyperalgesia must be present for the tricyclic antidepressants to blunt perception of visceral distension. This would define an important difference in mechanisms of analgesia of the tricyclics in the chronic somatic and visceral pain syndromes. Preliminary studies to address this possibility suggest that this is not the case. In a study of patients with functional dyspepsia, amitriptyline had no effect on perception of gastric distension but reduced overall dyspeptic symptoms (21). A second explanation is that tricyclic agents act on different anatomic sites in patients with somatic and gastrointestinal visceral pain. Recent investigations using positron emission tomography suggest the presence of abnormal central neural processing of visceral pain in IBS patients in different brain regions than with somatic pain (33, 37). It is conceivable that the dose of amitriptyline used in this investigation was too low to blunt visceral afferent function. However, many studies demonstrate analgesic effects at doses as low as 25 mg, and in the largest report of the use of antidepressant agents in IBS, most patients achieved symptom improvement at a median dose of 50 mg (5, 20). Thus, if this dose is effective for clinical control of symptoms and if it were to act via blunting of visceral hyperalgesia, one would expect a more prominent effect than was observed in the present study. It is also conceivable that the course of medication was too short; however, most investigations suggest that when used for analgesia the tricyclic agents exhibit efficacy within weeks (11). Furthermore, the ability of amitriptyline to blunt perception of cutaneous electrical stimulation in our volunteers indicated that sufficient time was provided for the drug to produce analgesia. Nonetheless, these alternate explanations are worthy of further investigation.

In conclusion, the tricyclic antidepressant agent amitriptyline reduces perception of innocuous and noxious cutaneous electrical stimulation but does not affect rectal or esophageal perception or compliance in healthy volunteers. These results indicate differential effects of amitriptyline on somatic and visceral afferent function and provide insight into the efficacy of tricyclic antidepressants in the treatment of IBS and NCCP.

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REFERENCES

1. Anderson, O. K., L. M. Jensen, J. Brennum, and L. Arendt-Nielsen. Evidence for central summation of C and A- δ nociceptive activity in man. *Pain* 59: 273–280, 1994.
2. Bardhan, K., G. Bodemar, H. Geldof, E. Schutz, C. Snell, and B. Darekar. A double-blind, placebo-controlled study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome (IBS) (Abstract). *Gastroenterology* 110: A630, 1996.
3. Chapman, W. P., R. Herrera, and C. M. Jones. A comparison of pain produced experimentally in lower esophagus, common bile duct, and upper small intestine with pain experienced by patients with diseases of the biliary tract and pancreas. *Surg. Gynecol. Obstet.* 89: 573–582, 1949.
4. Clouse, R. E., P. J. Lustman, T. C. Eckert, D. M. Ferney, and L. S. Griffith. Low-dose trazodone for symptomatic patients with esophageal contraction abnormalities: double-blind, placebo-controlled trial. *Gastroenterology* 92: 1027–1036, 1986.
5. Clouse, R. E., P. J. Lustman, R. A. Geisman, and D. H. Alpers. Antidepressant therapy in 138 patients with irritable bowel syndrome: a five-year clinical experience. *Aliment. Pharmacol. Ther.* 8: 409–416, 1994.
6. Coffin, B., D. Bouhassira, R. Chollet, B. Fraitag, C. de Meynard, J. Geneve, M. Lemann, J. C. Willer, and R. Jian. Effect of the kappa agonist fedotozine on perception of gastric distention in healthy humans. *Aliment. Pharmacol. Ther.* 10: 919–925, 1996.
7. Courteix, C., M. Bardin, C. Chantelauze, J. Lavarenne, and A. Eschaliier. Study of the sensitivity of the diabetes-induced pain model in rats to a range of analgesics. *Pain* 57: 153–160, 1994.
8. Dapoigny, M., J. L. Abitbol, and B. Fraitag. Efficacy of peripheral kappa agonist fedotozine versus placebo in treatment of irritable bowel syndrome. A multicenter dose-response study. *Dig. Dis. Sci.* 40: 2244–2249, 1995.
9. Delvaux, M., D. Louvel, B. Scherrer, B. Fraitag, and J. Frexinos. The κ -agonist fedotozine increases thresholds of first sensation and pain perception to colonic distention in patients with irritable bowel syndrome (Abstract). *Gastroenterology* 108: A590, 1995.
10. Dirksen, R., D. van Diejen, E. L. van Luijtelaaar, and L. H. Booij. Site- and test-dependent antinociceptive efficacy of amitriptyline in rats. *Pharmacol. Biochem. Behav.* 47: 21–26, 1994.
11. Egbunike, I. G., and B. J. Chaffee. Antidepressants in the management of chronic pain syndromes. *Pharmacotherapy* 10: 262–270, 1990.
12. Eide, P. K., and K. Hole. Acute and chronic treatment with selective serotonin uptake inhibitors in mice: effects on nociceptive sensitivity and response to 5-methoxy-*N,N*-dimethyltryptamine. *Pain* 32: 333–340, 1988.
13. Eija, K., T. Tiina, and N. J. Pertti. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain* 64: 293–302, 1996.
14. Greenbaum, D. S., J. E. Mayle, L. E. Vanegeren, J. A. Jerome, J. W. Mayor, R. B. Greenbaum, R. W. Matson, G. E. Stein, H. A. Dean, N. A. Halvorsen, and L. W. Rosen. The effects of desipramine on IBS compared with atropine and placebo. *Dig. Dis. Sci.* 32: 257–266, 1987.
15. Hasler, W. L., and C. Owyang. Irritable bowel syndrome. In: *Textbook of Gastroenterology* (2nd ed.), edited by T. Yamada. Philadelphia, PA: Lippincott, 1995, p. 1832–1855.
16. Hasler, W. L., H. C. Soudah, and C. Owyang. Somatostatin analog inhibits afferent pathways mediating perception of rectal distention. *Gastroenterology* 104: 1390–1397, 1993.
17. Hasler, W. L., H. C. Soudah, and C. Owyang. Somatostatin analog inhibits afferent response to rectal distention in diarrheapredominant irritable bowel syndrome patients. *J. Pharmacol. Exp. Ther.* 268: 1206–1211, 1994.
18. Magni, G. The use of antidepressants in the treatment of chronic pain. A review of the current evidence. *Drugs* 42: 730–748, 1991.
19. Max, M. B., S. A. Lynch, J. Muir, S. E. Shoaf, B. Smoller, and R. Dubner. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N. Engl. J. Med.* 326: 1250–1256, 1992.
20. McQuay, H. J., D. Carroll, and C. J. Glynn. Low dose amitriptyline in the treatment of chronic pain. *Anaesthesia* 47: 646–652, 1992.
21. Mertz, H. R., R. Fass, T. Hirsh, F. Yan-Go, and E. A. Mayer. Amitriptyline for functional dyspepsia: effect on symptoms,

- gastric sensitivity and sleep (Abstract). *Gastroenterology* 108: A649, 1995.
22. **Mertz, H., B. Naliboff, J. Munakata, N. Niazi, and E. A. Mayer.** Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterology* 109: 40-52, 1995.
 23. **Myren, J., B. Lovland, S. E. Larssen, and S. Larsen.** Psychopharmacologic drugs in the treatment of the irritable bowel syndrome. A double blind study of the effect of trimipramine. *Ann. Gastroenterol. Hepatol.* 20: 117-123, 1984.
 24. **Poulsen, L., L. Arendt-Nielsen, K. Brosen, K. K. Nielsen, L. F. Gram, and S. H. Sindrup.** The hypoalgesic effect of imipramine in different human experimental pain models. *Pain* 60: 287-293, 1995.
 25. **Prior, A., and N. W. Read.** Reduction of rectal sensitivity and post-prandial motility by granisetron, a 5-HT₃-receptor antagonist, in patients with irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 7: 175-180, 1993.
 26. **Raja, S. N., R. A. Meyer, and J. N. Campbell.** Peripheral mechanisms of somatic pain. *Anesthesiology* 68: 571-590, 1988.
 27. **Rani, P. U., M. U. Naidu, V. B. Prasad, T. R. Rao, and J. C. Shobha.** An evaluation of antidepressants in rheumatic pain conditions. *Anesth. Analg.* 83: 371-375, 1996.
 28. **Read, N. W., J. L. Abitbol, K. D. Bardhan, P. J. Whorwell, and B. Fraitag.** Efficacy and safety of the peripheral kappa agonist fedotozine versus placebo in the treatment of functional dyspepsia. *Gut* 41: 717-718, 1997.
 29. **Richter, J. E., C. F. Barish, and D. O. Castell.** Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 91: 845-852, 1986.
 30. **Ritchie, J. A., and S. C. Truelove.** Comparison of various treatments for irritable bowel syndrome. *Br. J. Med.* 281: 1317-1319, 1980.
 31. **Rossi, A., and B. Decchi.** Flexibility of lower limb reflex responses to painful cutaneous stimulation in standing humans: evidence for load-dependent modulation. *J. Physiol. (Lond.)* 481: 521-532, 1994.
 32. **Sengupta, J. N., and G. F. Gebhart.** Characterization of mechanosensitive pelvic nerve afferent fibers innervating the colon of the rat. *J. Neurophysiol.* 71: 2046-2060, 1994.
 33. **Silverman, D. H. S., J. A. Munakata, H. Ennes, M. A. Mandelkern, C. K. Hoh, and E. A. Mayer.** Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology* 112: 66-72, 1997.
 34. **Spiegel, K., R. Kalb, and G. W. Pasternak.** Analgesic activity of tricyclic antidepressants. *Ann. Neurol.* 13: 462-465, 1983.
 35. **Steinhart, M. J., P. Y. Wong, and M. L. Zarr.** Therapeutic usefulness of amitriptyline in spastic colon syndrome. *Int. J. Psychiatry Med.* 11: 45-57, 1981-1982.
 36. **Swarbrick, E. T., J. E. Hegarty, L. Bat, C. B. Williams, and A. M. Dawson.** Site of pain from the irritable bowel. *Lancet* 2: 443-446, 1980.
 37. **Talbot, J. D., S. Marrett, A. C. Evans, E. Meyer, M. C. Bushnell, and G. H. Duncan.** Multiple representations of pain in human cerebral cortex. *Science* 255: 215-216, 1992.
 38. **Whitehead, W. E., B. T. Engel, and M. M. Schuster.** Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Dig. Dis. Sci.* 25: 404-413, 1980.

