Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study

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Esfandyari T, Camilleri M, Busciglio I, Burton D, Baxter K, Zinsmeister AR. Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. *Am J Physiol Gastrointest Liver Physiol* 293: G137–G145, 2007. First published March 29, 2007; doi:10.1152/ajpgi.00565.2006.—Cannabinoid receptors (CBR) are located on cholinergic neurons in the brain stem, stomach, and colon. CBR stimulation inhibits motility in rodents. Effects in humans are unclear. Dronabinol (DRO), a nonselective CBR agonist, inhibits colonic motility and sensation. The aim of this study was to compare effects of DRO and placebo (PLA) on colonic motility and sensation in healthy volunteers. Fifty-two volunteers were randomly assigned (double-blind) to a single dose of 7.5 mg DRO or PLA postoperative with concealed allocation. A balloon-manometric assembly placed into the descending colon allowed assessment of colonic compliance, motility, tone, and sensation before and 1 h after oral ingestion of medication, and during fasting, and for 1 h after 1,000-kcal meal. There was an overall significant increase in colonic compliance ($P = 0.045$), a borderline effect of relaxation in fasting colonic tone ($P = 0.096$), inhibition of postprandial colonic tone ($P = 0.048$), and inhibition of fasting and postprandial phasic pressure ($P = 0.008$ and 0.030, respectively). While DRO did not significantly alter thresholds for first gas or pain sensation, there was an increase in sensory rating for pain during random phasic distensions at all pressures tested and in both genders ($P = 0.024$). In conclusion, in humans the nonselective CBR agonist, DRO, relaxes the colon and reduces postprandial colonic motility and tone. Increase in sensation ratings to distension in the presence of relaxation of the colon suggests central modulation of perception. The potential for CBR to modulate colonic motor function in diarrheal disease such as irritable bowel syndrome deserves further study.

dronabinol; compliance; tone; pain

THE EFFECTS OF CANNABINOIDS are mediated primarily through cannabinoid receptors. Two types of G protein-coupled cannabinoid receptors, named CB_1 and CB_2, have been identified and cloned (18, 21, 24). Recent data suggest the presence of a third, as yet uncloned, cannabinoid receptor (1). CB_1 immunoreactivity is located on normal colonic epithelium, smooth muscle, and the myenteric plexus, whereas CB_1 and CB_2 receptors are expressed in plasma cells (32).

Given the great variability in the activity of the endocannabinoid system between species, and in different regions of the gastrointestinal (GI) tract of the same species, it is difficult to predict effects in human colon. In mice, endocannabinoids acting on myenteric CB_1 receptors tonically inhibit colonic propulsion (27). There is evidence of a direct role for cannabinoids in the modulation of motor activity in muscle strips from human colon (16). Activation of CB_1 receptors coupled to cholinergic motor neurons inhibits excitatory nerve transmission in colonic human colonic circular muscle (16).

In this study, we assessed the effect of a nonselective cannabinoid agonist, dronabinol, on colonic sensory and motor functions of healthy volunteers. Dronabinol is FDA-approved as an antiemetic and appetite-stimulating medication. In a previous study from our laboratory (9) performed in healthy adults, dronabinol, 5 mg b.i.d., delayed gastric emptying, although this effect was mainly observed in female subjects. In the same study, colonic transit was not significantly different with the same dose of dronabinol compared with placebo.

The aim of the current study was to compare the acute effects of dronabinol, 7.5 mg, and placebo postoperative on colonic sensory and motor functions in healthy adults.

MATERIALS AND METHODS

Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group study of the pharmacodynamic effects of dronabinol on colonic sensory and motor function of healthy human volunteers between the ages of 18 and 65 yr and body mass index between 18 and 32 kg/m². The study was conducted in the General Clinical Research Center at Mayo Clinic in Rochester, MN. The study was approved by Mayo Clinic Institutional Review Board and a data safety monitoring plan was established before starting the study.

Participants

Participants were recruited from the local community by public advertisement. They underwent screening using validated questionnaires to ensure they had no current or chronic gastrointestinal symptoms or significant psychiatric dysfunction (29, 33). All candidates who met the eligibility criteria for the study underwent a complete history and physical examination before enrollment. The trial flow is summarized in Fig. 1. Ultimately, 52 healthy participants were enrolled, from an initial 61 volunteers recruited by public advertisement. All females of childbearing potential had to have negative pregnancy test within 48 h of study. Participants were randomized to one dose of placebo, or dronabinol, 7.5 mg, taken with water at the study center under supervision of study staff. Colonic motility data from 12 participants were lost due to computer malfunction before storage of the data and its analysis; therefore, 12 more participants were recruited to complete the requisite 20 in each group, as required by the prestudy power calculation. By chance, the ran-
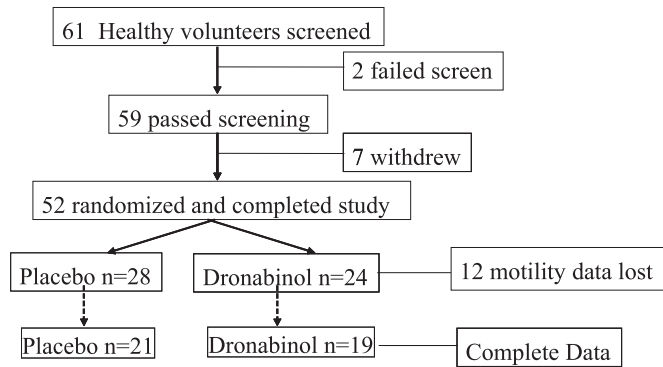
Fig. 1. Trial flow chart.

domization procedure led to 21 in one group and 19 in the other. However, data on sensation were available from all 52 participants randomized in the study and, following intent-to-treat principles, all the data available were included in the analyses.

Allocation was concealed, and investigators were blinded to all treatment assignments until study blind was communicated to the study statistician by the research pharmacist.

Experimental Protocol

After overnight bowel preparation using a standard polyethylene glycol-containing electrolyte solution to induce cleansing, a balloon-manometry assembly was placed in the descending colon of each participant with the aid of colonoscopy and fluoroscopy. After 30-min rest, fasting colonic tone, colonic compliance, and colonic sensation were tested. Then, the study medication was ingested, and 1 h later the same colonic functions were assessed in the fasting state; subsequently, colonic tone was measured for 1 h after a standardized meal. Figure 2 outlines the experimental protocol. The final position of the barostatically controlled balloon was confirmed fluoroscopically and was in the upper and lower descending colon in 31 (14 dronabinol, 17 placebo) and 9 (5 dronabinol, 4 placebo) participants, respectively.

Pharmacology of Dronabinol

Dronabinol is a synthetic delta-9-tetrahydrocannabinol (Δ^9-THC). It is a nonselective cannabinoid agonist; 90–95% of the dose is absorbed after a single oral dose (23). Due to the combined effects of first-pass hepatic metabolism and high lipid solubility, only 10–20% of the administered oral dose reaches the systemic circulation. After

oral administration, onset of action is approximately after 0.5 to 1 h and peak effect is at 2 to 4 h. The elimination phase follows a two-compartment model, with an initial half-life of ~4 h and a terminal half-life of 25 to 36 h. Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Biliary excretion is the major route of elimination.

The dose of dronabinol selected for this study (7.5 mg) was based on the high frequency of central adverse effects such as drowsiness and lightheadedness noted with the 5-mg b.i.d. dose of dronabinol in the prior study (9), and this is close to the starting dose level used in clinical practice (range 2.5 to 40 mg/day) for AIDS-cachexia or chemotherapy-induced emesis. The dose selected was therefore a balanced one, which took into consideration the fact that our prior study showed that 5 mg b.i.d. already demonstrated an effect on gastric emptying (9), and the concern that assessment of sensation of colonic distension might be compromised by unblinding due to central side effects with a much higher dose.

At the time of the study, and even to date, there is no selective CBR1 or CBR2 receptor antagonist approved for use in humans in the United States.

Colonic Tube Placement

Studies were performed as previously described in the literature from our laboratory over more than 10 years (3). All subjects presented on the study day after an overnight bowel preparation with an oral colonic lavage solution (NuLytely; Braintree Laboratories, Braintree, MA) and a 12-h fast. Flexible colonoscopy was performed without sedation to evaluate the left side of the colon and to place a teflon-coated guidewire (Microvasive, Hobbs Medical, Stafford Springs, CT) into the colon beyond the splenic flexure. The colon was deflated as the colonoscope was withdrawn. The barostat catheter incorporating six manometric point sensors was introduced into the colon over the guidewire and was positioned under fluoroscopic control with the polyethylene balloon [10-cm-long cylinder with a maximum volume of 600 ml (MVI Scientific, Ontario, Canada)] in the mid-descending or upper sigmoid colon. The catheter was connected to a rigid-piston barostat (Mayo Clinic, Rochester, MN) by means of a double-lumen tube for balloon distention and intraballoon pressure and volume measurement. To decrease the effects of the abdominal viscera on the intracolonic balloon volume, the study participants remained in a semiprone position (left side up) for the duration of the study. A pneumobelt was placed around the abdomen at the level of the lower costal margin to identify and exclude artifact during movement and coughing. Intracolonic balloon volumes were measured

Fig. 2. Experimental protocol. Stepwise distension during ascending method of limits is used to appraise thresholds and compliance and random-order phasic distensions to obtain sensory ratings. Motor function was tested before drug, after drug, and after meal ingestion.
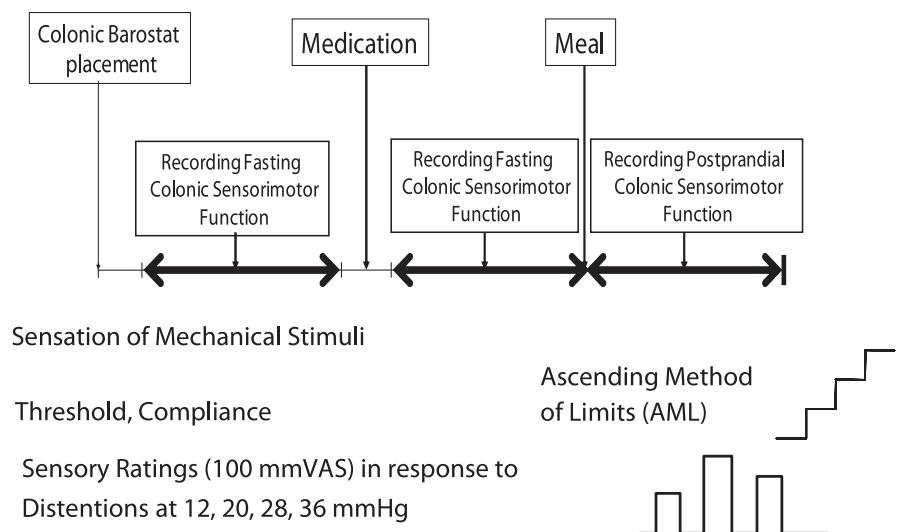
throughout the study. The six water-perfused pneumohydraulic sensors were located at 5-cm intervals along the same tube on which the barostat balloon was mounted.

After an initial inflation to a volume of 75 ml to ensure unfolding of the balloon, it was deflated and reinflated with 1-mmHg increments of pressure. The operating pressure was defined as 2 mmHg above the minimal distension pressure at which respiratory excursions were clearly recorded from the barostat tracing.

Assessment of Colonic Motor and Sensory Function

Previous studies showed that an initial "conditioning" distension to 20 mmHg renders subsequent assessments of compliance and perception more reproducible (15a). Therefore, a conditioning distention from 0 to 20 mmHg in increments of 4 mmHg every 15 s was performed over a period of 75 s. After an equilibration period of 10 min, colonic compliance was assessed by increasing the intraballoon pressure in a ramp-like procedure in 4-mmHg increments at 30-s intervals. During the assessment of colonic compliance, participants were asked to report the threshold pressures at which they had first perception, gas, and pain.

After the assessment of compliance and another 10-min equilibration period, fasting colonic tone was measured at the operating pressure for a period of 10 min. Randomized-order phasic distensions were then applied at 12, 20, 28, and 36 mmHg above the operating pressure to measure the sensation ratings of gas and pain. Each distention lasted 1 min and was followed by an equilibration period at the operating pressure for 2 min. A visual analog scale [VAS (0 = no anxiety/stress; 10 = maximum anxiety/stress)] was used to assess the level of anxiety or stress experienced by each subject because it has been shown previously to be a potentially significant covariate in the assessment of visceral sensation scores (3, 10a). Thus colonic compliance, fasting tone, pressure thresholds for first perception, gas, and pain, and VAS scores of gas and pain during phasic distensions were measured before receiving the study medication and 1 h after drug administration. After the postdrug assessment of the above mentioned parameters, a standard liquid, high-fat, 1,000-kcal meal (750-ml chocolate milkshake, 53% fat, 35% carbohydrate, 12% protein) was administered to induce the colonic response to feeding over 60 min. When the recording was finished, the balloon was deflated and the tube was removed by gentle traction.

Data Analysis

Colonic compliance. Because colonic pressure-volume relationships are sigmoidal rather than linear, compliance was summarized by a power exponential model, plotting the observed volume at each pressure divided by the maximum observed volume as a function of 1/pressure, as in previous studies (3, 8): $P_{vol} = R + exp\{-[k \times (1/Pr)]^\beta\}$, where P_{vol} is the proportionate volume (vol/V_{max}, V_{max} is the maximum volume in the compliance assessment), Pr is the pressure, and R is the observed ratio of minimum volume to maximum volume. The summary parameters estimated for this model of compliance, k (slope) and β (overall shape of the curve), were used to calculate $Pr_{1/2}$, the pressure producing the half-maximum volume on the pressure-volume curve. The value for k (slope) represents the change in volume as a function of 1/Pr at any given point.

Colonic motor function. Colonic tone was assessed operationally as in the prior literature as the intracolonic balloon volume measured at the operating pressure. Tone was calculated by the baseline colonic volumes measured throughout the period of interest during fasting or after the meal (3). Using computer-based 5-min mean volumes for the periods of interest and using the mean of each 5-min observation in those periods, changes in colonic tone were calculated as absolute volume changes during fasting in response to the study medication and as the symmetric percent change in volume postprandially (3).

Colonic manometry. The same computer program was used to measure the postprandial phasic motor activity in the proximal and distal three manometric sensors. Because of variation in the location of the barostat balloon in the upper or lower descending colon, the phasic activity was summarized in each individual for the three sensors that were located in the distal descending and sigmoid colon. Data were compared for the fasting period vs. the four 15-min periods after the 1,000-kcal meal was ingested. Colonic phasic pressure activity was summarized as a motility index (MI) where MI = log_e (sum of amplitudes * number of contractions + 1).

Colonic sensation. We recorded the pressure thresholds at which participants reported first perception, gas, and pain during the assessment of colonic compliance (ramp distention), and the intensity ratings were recorded for gas and pain on 100-mm VAS scales during phasic distensions. The stress and anxiety scores were used as covariates in the analysis of the effects on sensation.

Power Assessment and Statistical Analysis

The planned sample size total of 40 (with 20 per group) had 80% power (at a 2-sided α level of 0.05) to detect 36% differences in the primary motor endpoint (fasting colonic tone) and 52–60% differences in pain and gas and sensory ratings in response to balloon distensions at 28 and 36 mmHg using a two-sample *t*-test.

The study statistician and the entire research team were blinded to treatment allocation until all analyses of motor and sensory endpoints had been completed. An analysis of covariance (ANCOVA) was used to compare treatment effects on colonic tone and compliance, incorporating gender, body mass index (BMI), and the corresponding "baseline" or predrug value as covariates. We also included a treatment by gender interaction.

A proportional hazards regression analysis was used to assess treatment effects on sensation thresholds, incorporating gender, BMI, and the corresponding pretreatment sensory threshold value as covariates. A potential gender by treatment interaction effect was also examined.

A repeated-measures ANCOVA was used to assess treatment effects on VAS gas and pain sensory ratings. The repeated measures corresponded to the multiple pressure distensions, done in random order, in each participant. The model included the corresponding average (over all 4 distensions) sensory rating during the predrug study, the postdrug pressure distension level, and gender as covariates, along with gender by treatment, pressure by treatment, and gender by pressure by treatment interaction terms.

RESULTS

Participants and Compliance with Medication

Sixty-one participants volunteered for the study, two failed screening, and seven withdrew after reading the specific details of the studies in the consent form. Fifty-two healthy volunteers meeting the entry criteria were screened and participated in the study. Twenty-eight volunteers randomly received placebo and 24 volunteers received 7.5 mg dronabinol. Table 1 summarizes patients' demographics by treatment group. No clinically important differences in age, sex, BMI, barostat operating pressure, or predrug fasting colonic tone were observed between treatment groups (28 vs. 24 with sensation data or 21 vs. 19 with motility data). All sensation data are available for the entire cohort of 52 participants (in which pressure and volume were recorded electronically); however, note that $n = 19$ for dronabinol and $n = 21$ for placebo for the compliance, tone, and phasic pressure activity data as a result of computer loss of data from 12 participants. Thus sensation data were analyzed for all 52 participants and motility data for 40 participants.

Table 1. *Participants' baseline characteristics*

	Placebo (*n* = 28)	Dronabinol (*n* = 24)
Age, yr	34.2 ± 2.5	36.8 ± 2.8
# Males, % [mean age]	12 (43%) [37]	10 (42%) [37]
# Females, % [mean age]	16 (57%) [32]	14 (58%) [36]
BMI, kg/m^2	24.5 ± 0.7	25.3 ± 0.7
Operating pressure, mmHg	10.7 ± 0.4	11.1 ± 0.4
Predrug fasting colonic tone, ml	89.1 ± 6.0	88.1 ± 6.8

Values are means $\pm$ SE, unless otherwise noted. BMI, body mass index.

Effects on Colonic Compliance

There were overall treatment effects on colonic compliance ($P = 0.045$) with dronabinol. The effect on compliance was most pronounced in females (Fig. 3). The reduction in $Pr_{1/2}$ reflects an increase in compliance of the colon in response to dronabinol.

Effects on Fasting and Postprandial Colonic Tone

The effect of dronabinol on fasting colonic tone was borderline ($P = 0.096$; Table 2 and Figs. 4 and 5). There was an overall treatment effect on postprandial ($P = 0.048$) colonic tone in response to dronabinol. Dronabinol significantly reduced the decrease in intracolonic balloon volume after ingestion of a standard meal, suggesting a postprandial inhibition of the normal increase in the tone of the colon after the meal.

Effect on Phasic Colon Contractile Activity

Phasic contractility during fasting and postprandially was compared in the two treatment groups using the three sensors located in the sigmoid and descending colon as recorded in all individuals. Before treatment, fasting colonic motility was not different in the two groups. Dronabinol tended to reduce postdrug colonic motility indexes ($P = 0.078$; Fig. 6). Before the meal, the effect of dronabinol on phasic motility was significant ($P = 0.008$). Similarly, dronabinol was associated with a significantly reduced increase in colonic phasic pressure activity after the meal. This was noted for the mean 1-h ($P = 0.030$; Fig. 6) and individual 15-min motility indexes in the entire first postprandial hour (Fig. 7; note: $n = 19$ for dronabinol and $n = 21$ for placebo in this figure as a result of loss of data from 12 participants).

Effects on Colonic Sensory Function during Phasic and Ramp Distensions

Sensation thresholds for gas and pain were not different in the two treatment groups (Fig. 8). Sensation scores for pain in response to increasing pressures were significantly different among groups. Dronabinol increased sensory rating for pain during random phasic distensions at all pressures tested and in both genders ($P = 0.024$, overall treatment effect, repeated-measures ANCOVA; Table 3).

Fig. 3. Effect of dronabinol on colonic compliance. *A*: plots of pressure:volume curves based on the mean k and β of curves for male and female participants before (*left*) and after (*right*) treatment with placebo or dronabinol. Note the shift of the curve to the *left* in females treated with dronabinol indicating increased compliance. *B*: summary data show that dronabinol reduces pressure at half-maximal volume suggesting increase in colonic compliance (total *n* = 21, 9 male, 12 female; means $\pm$ SE). *$P < 0.05$, compared with corresponding placebo value (ANCOVA).
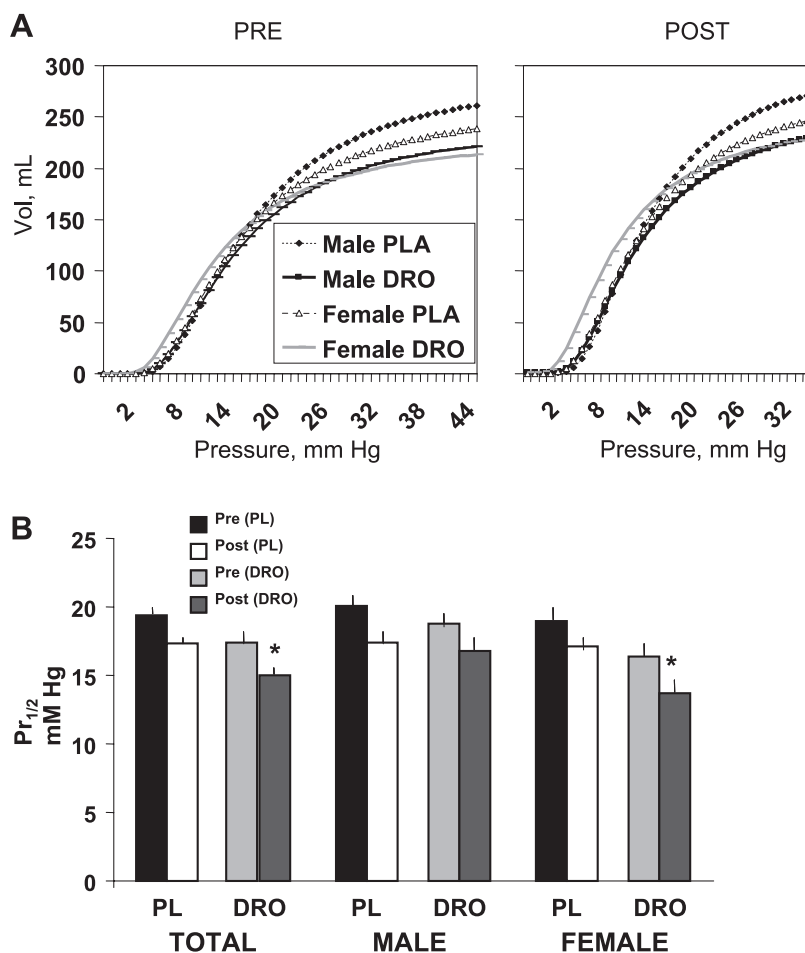
Table 2. *Effect of dronabinol on fasting and postprandial colonic tone*

	Placebo		Dronabinol	
	Pre	Post	Pre	Post
Colonic fasting tone	89.1±6.0	107.5±7.6	88.1±6.8	128.5±13.0
Colonic fasting tone, male	89.8±8.5	105.1±9.8	88.0±6.7	119.6±9.6
Colonic fasting tone, female	88.5±8.7	109.3±11.5	88.1±11.1	135.0±21.7
Colonic postprandial tone		64.3±6.5		88.0±9.4*
Colonic postprandial tone, male		60.3±6.5		90.3±16.4
Colonic postprandial tone, female		67.3±10.5		86.2±11.6

Values are means ± SE. *$P = 0.048$, analysis of covariance, adjusting for pretreatment fasting tone, BMI, and gender.

DISCUSSION

This study demonstrates cannabinoid modulation of colonic motility; specifically, dronabinol was associated with relaxation of the colon and inhibition of the increase in tone after the meal. Increased colonic compliance was predominantly due to a significant effect in females. We previously observed greater effect of dronabinol on gastric emptying prolongation in female healthy volunteers than in males (9).

Fig. 4. Effect of dronabinol on fasting (*A*) and postprandial (*B*) colonic tone. Note that, with placebo treatment, the meal induced a reduction in balloon volume in the colon under isobaric conditions, which is consistent with an increase in colonic tone. In contrast, dronabinol reduced the colonic contraction in response to the meal. *$P < 0.05$ compared with corresponding placebo value (ANCOVA).

A consistent finding in the current study is that dronabinol resulted in increased compliance, reduced fasting colonic tone, reduced postprandial colonic tone, and reduced phasic pressure response to the ingestion of a meal. All of these results are internally consistent and reflect the inhibition of excitatory motor or activation of inhibitory mechanisms. The fact that both compliance and fasting tone are relaxed also suggests that dronabinol inhibits a tonic excitatory input to the colonic muscle. In addition, dronabinol inhibited the response to feeding.

These features, as well as the known location of cannabinoid receptors on cholinergic neurons in the brain stem, stomach, and colon, suggest that the cannabinoid receptor agonist may be inhibiting central or enteric colonic muscle excitation, such as through cholinergic neurons. This suggests that cannabinoid receptor modulation may be a potential target for therapy in diseases associated with altered colonic motor function. Thus a cannabinoid receptor agonist may be effective in reducing postprandial stimulation of colonic propulsion, as occurs in some patients with diarrhea and urgency associated with irritable bowel syndrome or dysautonomia (6).

In fact, cannabidiol analogs devoid of the central effects on cannabinoid receptors have been proposed as potential therapies for diarrheal diseases (12, 13). In contrast, a cannabinoid receptor antagonist may oppose the inhibition of cholinergic mechanisms due to endogenous cannabinoids, thereby accelerating colonic transit or causing intestinal secretion and relieving constipation. Izzo et al. (19) showed in a mouse model that SR141716A (0.1–5 mg/kg ip), a cannabinoid CB_1-receptor antagonist, increased defecation, gastrointestinal transit, and fluid accumulation. These effects were inhibited by atropine (1 mg/kg ip) but not by the ganglion blocking agent hexamethonium or by antagonists of NK_1 and NK_2 receptors. Interestingly, in clinical trials using SR141716A or rimonabant for nicotine cessation or for the treatment of obesity, diarrhea was 2 to 2.4 times more frequent among those treated with the drug than with placebo, suggesting accelerated transit and/or enhanced secretion caused by CB_1 blockade (10, 30).

These observations lend support to the importance of cannabinoid receptors in the control of gastrointestinal function. The literature provides numerous studies using autoradiography, immunohistochemistry, and/or reverse transcription-polymerase chain reaction to demonstrate colocalization of CB_1 receptors with cholinergic neurons across the enteric nervous system, including sensory and interneuronal as well as motor neuron cell bodies of the myenteric plexus in several species, as recently comprehensively reviewed (26). These include mice, rats, guinea pigs, and pigs. CB_1 receptors are also colocalized with neuropeptide Y and vasoactive intes-
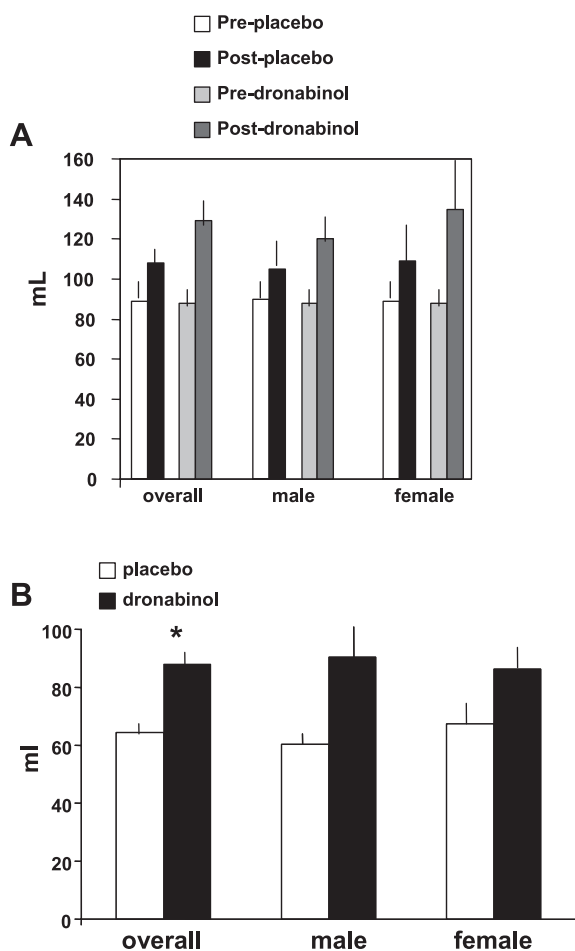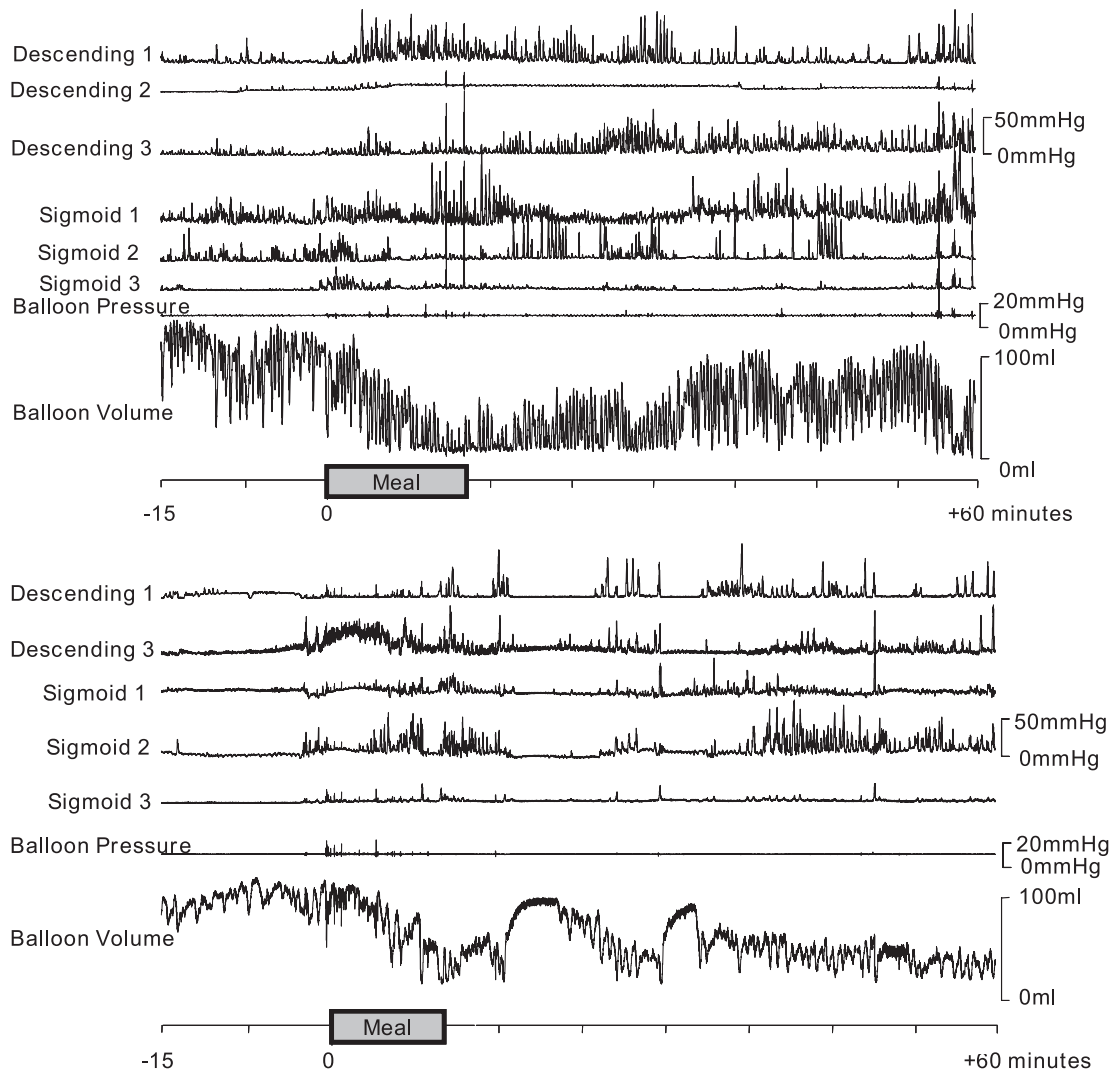
Fig. 5. Examples of the phasic activity and balloon volumes in the colon segment in response to placebo (*top*) or dronabinol (*bottom*) in 2 participants. Note that dronabinol treatment was associated with a reduced reduction in the barostat balloon volume and no change in the phasic pressure response of the colon following food ingestion. In contrast, the tone (baseline volume reduction) and phasic pressure response to the meal were significantly increased in the participant who received placebo.

tinal peptide in a small population of submucous plexus neurons (7, 20).

CB$_1$ receptor immunoreactivity was also demonstrated in normal human colonic epithelium, smooth muscle, and the myenteric plexus (32). Both CB$_1$ and CB$_2$ receptors were found on plasma cells in the lamina propria, whereas only CB$_2$ receptors were detectable on macrophages (32). Endocannabinoids are also present in the gastrointestinal tact. Indeed, the
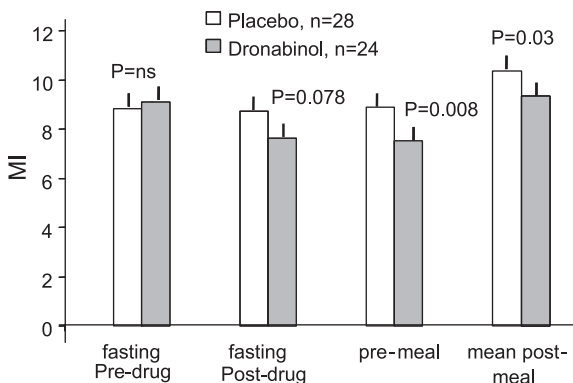

Fig. 6. Effect of dronabinol on colonic phasic motility in the fasting and postprandial period [MI = Ln (sum of amplitudes * number of contractions +1)].
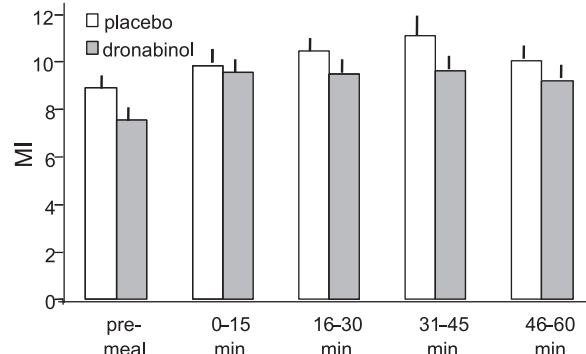

Fig. 7. Detailed 15-min postprandial colonic motility indexes are lower with dronabinol than placebo.
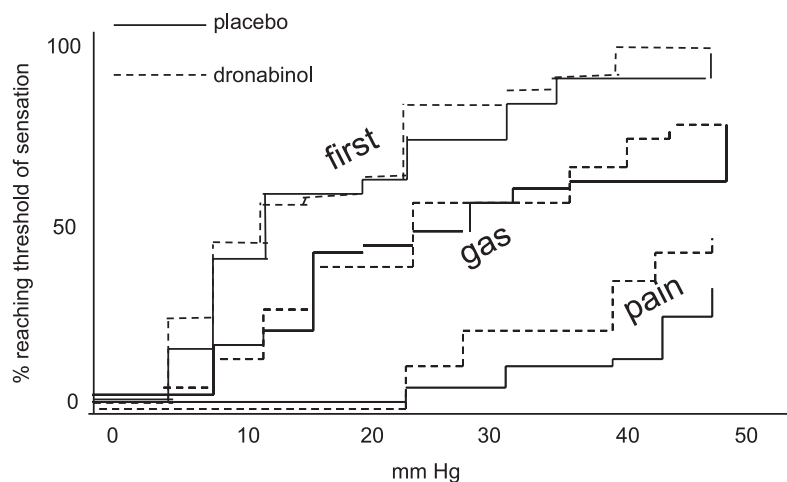
Fig. 8. Pain thresholds for first sensation, gas, and pain showing no significant difference in the placebo and dronabinol groups.

endocannabinoid 2-arachidonyl glycerol, 2-AG, was originally isolated from gut tissue (22), and the intestinal content of anandamide was found to be regulated by feeding status (14).

The significant effects on colonic tone and phasic pressure activity contrast with the lack of effect on colonic transit with a dose of dronabinol, 5 mg b.i.d., in our previous study in humans (9) rather than the 7.5-mg dose used in this study. It is important to note that colonic transit is a relatively insensitive method to evaluate motor function over a 48-h period. In contrast, the intraluminal measurement of colonic motor function allows evaluation of tone and phasic motility during fasting, pre- and postdrug, as well as in the first hour after a meal. It is important to note that all the motility measurements, that is compliance, fasting, and postprandial tone, and fasting and postprandial colonic phasic pressure activity are all inhibited by dronabinol, that is the effects on motor endpoints are consistent.

Postprandial tone is largely induced by the reflex activation of colonic motility through a vagally mediated pathway. Inhibition of postprandial colonic tone with dronabinol mimics the effects of a 5-HT$_3$ antagonist on colon motor function (25). However, the effects of dronabinol during fasting, such as the reduction in colonic phasic motor activity and the increased compliance, suggest that the cannabinoid receptor controls tone in the absence of vagal reflex activation and that effects of dronabinol on colonic motility may be mediated through central or peripheral (enteric) control mechanisms. This requires further study.

Given the relaxatory effect of dronabinol on the colon, it was surprising to find that phasic colonic distensions were associated with higher (rather than lower) sensory ratings. An increase in sensation would be contrary to be expected if the sensations were determined principally by the level of tone in the colon. An additional precaution taken in our study was to use pressure-based distensions to avoid the erroneous interpretation of sensory changes with volume-based sensory ratings, as a result of the increased compliance or relaxation of the colon during fasting. It is also relevant to point out that only the sensory rating of pain was increased by dronabinol, with no effect on other endpoints, such as the sensory rating of gas, and thresholds for first sensation, gas or pain. Given the wide coefficient of variation in sensory thresholds and ratings in such distension studies (8), we perceive that the effects of cannabinoid modulation on colonic sensation should be interpreted with caution and that further studies using selective antagonists active on cannabinoid receptors are required before any definitive conclusions can be drawn on the effects of dronabinol on visceral sensation.

The increased pain perception with dronabinol is difficult to explain, given the reported antinociceptive effects with cannabinoids which have been extensively reviewed elsewhere (11). It is worth noting that CB$_1$ and CB$_2$ antagonists did not alter basal colonic sensitivity and that CB$_1$ antagonist increased colitis-induced hyperalgesia in rats with trinitro-benzene sulfonic acid-induced colitis (28). Given that our experiments were conducted in healthy volunteers with uninflamed colon, it is conceivable that the analgesic effects of the CBR agonist were not observed and that increased awareness (4) led to the increased sensory ratings in our studies.

It is also well-known that the analgesic effect of THC and other cannabinoids in humans is less clear. A meta-analysis of earlier studies suggested that cannabinoids were not more effective than codeine in controlling pain, and their use was associated with numerous undesirable, dose-limiting central

Table 3. *Effect of dronabinol on colonic sensory function*

	Placebo		Dronabinol	
	Pre	Post	Pre	Post
Sensory rating pain 20 mmHg, mm VAS	32.1±5.2	29.7±4.5	31.2±4.8	33.3±4.6
Sensory rating pain 28 mmHg, mm VAS	43.8±4.9	35.2±4.5	32.3±4.3	41.1±5.2*
Sensory rating pain 36 mmHg, mm VAS	43.6±5	41.5±5.2	40.1±5.0	52.8±5.6*

Values are means ± SE. Note that pain ratings during random-order phasic distensions are higher with dronabinol relative to placebo [*$P < 0.05$ vs. placebo (ANCOVA)]. VAS, visual analog scale.

nervous system side effects (5). Several more recent randomized, controlled studies show mixed results in neuropathic pain syndromes (2, 4, 17). Overall, the increased sensory ratings, despite the increased colonic compliance, suggest that the increased sensitivity reflects heightened sensory awareness, possibly of central origin. Increased awareness of surroundings was reported more frequently in patients receiving Δ^9-THC (4). Sanson et al. (28) suggest that the effects on sensation are mediated peripherally.

Finally, it is conceivable that the increase in pain ratings during colonic distension with the acute administration of dronabinol results from alterations in the central mechanisms involved in downregulation of the dorsal horn neurons. The latter mediate peripheral afferent sensations ascending to the brain centers that are involved in pain perception. Cannabinoids produce antinociception, in part, by modulating descending noradrenergic systems; however, experimentally, this suppression of pain behavior is short lived and demonstrable for the first 10 min, but not for the 40 to 60 min after intraperitoneal administration of a cannabinoid agonist, WIN55,212-2 (15). Further studies are needed to explore the nociceptive and antinociceptive effects of cannabinoid receptor modulation in the sensory neuraxis in humans. Such apparently paradoxical increases or decreases in neural activity in the central nervous system are also manifested by the observations that dronabinol may have either proconvulsant or anticonvulsant activity.

In summary, our study shows, for the first time, that cannabinoids affect colonic motor and sensory functions in humans. These effects may be harnessed with novel and selective agonists and antagonists to the cannabinoid receptors. Thus this class of compounds may be potentially used in the treatment of gastrointestinal motility disorders, in addition to the potential use in the treatment of obesity.

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