Intraluminal capsaicin does not affect fluid and electrolyte absorption in the human jejunum but does cause pain

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Abstract

Background—Stimulation of sensory nerves with capsaicin regulates ion transport in the small intestine in animal experiments.

Aim—To investigate whether sensory nerves that are stimulated by capsaicin administration influence fluid and electrolyte absorption in the human jejunum in vivo.

Method—Intestinal perfusion studies were performed in 12 healthy subjects using a four lumen tube with a proximal occlusion balloon and a plasma-like electrolyte solution. After an initial control period, 5 (n = 3), 10 (n = 8), or 50 (n = 1) µg/ml capsaicin was added to the perfusate, and this was followed by a final control period. Rates of absorption of water, sodium, potassium, chloride, and bicarbonate were determined in a 30 cm segment of jejunum using a non-absorbable volume marker.

Results—At all three concentrations of capsaicin there were no significant changes in water and electrolyte absorption as compared with control periods. Two subjects who received 10 µg/ml and the subject receiving 50 µg/ml experienced crampy abdominal pain.

Conclusion—The results do not support the hypothesis that capsaicin sensitive afferent nerves are involved in the physiological regulation of net absorption or secretion across the human jejunal mucosa. Chemical stimulation of these nerves, however, gives rise to abdominal pain.

(Gut 1998;43:252-255)

Keywords: capsaicin; sensory nerves; axon reflex; motility; jejunum

regulate intestinal secretion, motility, and circulation.³

Involvement of sensory nerves in the regulation of intestinal secretion has been shown in various animal species. In these studies, sensory nerves were stimulated by electrical field or capsaicin. Chloride secretion in the ileum of the rabbit and guinea pig is enhanced by electrical field stimulation⁴⁻⁶ and by capsaicin.⁷ Capsaicin has also been shown to stimulate nutrient absorption in rats.⁸ It has been suggested that capsaicin sensitive nerves regulate ion transport in the gastrointestinal tract by release of neurotransmitters that activate submucosal secretomotor neurons.⁷ Capsaicin sensitive neurons have also been shown to mediate the pathological hypersecretion caused by *Escherichia coli* enterotoxin in the rat intestine⁹ and by *Clostridium difficile* toxin A in the rat ileum.¹⁰

In the human small intestine, capsaicin sensitive neurons have been shown to affect small intestinal motility in vitro,¹¹⁻¹³ but there are no data on their effect on intestinal secretion and on their effects in vivo. The aim of this study was to test the hypothesis that luminal capsaicin administration increases chloride secretion in the human jejunum in vivo.

Methods

EXPERIMENTAL SUBJECTS

Studies were carried out in 12 healthy men, aged 20-36, mean age 25. They were recruited by public advertisement and none had a history of gastrointestinal disease or abdominal surgery other than appendectomy. All subjects gave written informed consent. The study was approved by the ethics committee of Karl Franzens University of Graz.

EXPERIMENTAL DESIGN AND PROCEDURE

For intestinal perfusion, a tube assembly (outer diameter 7 mm) was used that consisted of five tubes that were bonded together with tetrahydrofuran (Sigma Chemical Corp, St Louis, Missouri, USA). One tube was connected to a balloon which was used to occlude the intestinal lumen proximal to the site of infusion. Three tubes were radio-opaque to allow fluoroscopic location of the assembly; their distal ends were immediately distal to the occluding balloon (perfusion site) and 30 cm and 60 cm distal to the balloon (sampling sites). The length of the test segment (between proximal and distal sampling site) was 30 cm. An additional lumen was used to remove endogenous secretions proximal to the occluding balloon.

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Accepted for publication
25 February 1998

Figure 1 Experimental design.

After a 12 hour fast, volunteers swallowed the tube assembly. The position of the assembly was confirmed by fluoroscopy. The infusion site was located at the ligament of Treitz. With the tube in the right position, the occluding balloon was inflated with 60 ml of air and perfusion was started. None of the subjects experienced any sensation as the balloon was inflated. As shown in fig 1, perfusion was performed for three 60 minute test periods, which were preceded by 30 minute equilibration periods. The first and the third test period were used as intraindividual controls. The second test period was used to assess the effect of capsaicin. During the equilibration periods the samples were discarded. During each of the control and test periods, samples were collected separately for three consecutive 20 minute periods.

A plasma-like electrolyte solution containing 135 mM sodium, 5 mM potassium, 110 mM chloride, 30 mM bicarbonate, and 2 g/l polyethylene glycol was perfused at an infusion rate of 10 ml/min using a peristaltic pump. The rate of aspiration at the two sampling sites was 1.5 ml/min. During the capsaicin test period, 5 (n = 3), 10 (n = 8), or 50 (n = 1) µg/ml capsaicin (Sigma Chemical Corp) was added to the perfusate for 90 minutes—that is, a 30 minute equilibration and a 60 minute test period.

Intestinal samples were analysed for sodium, potassium, chloride, and bicarbonate (as total CO₂) concentration using an automated analyser (Synchron Clinical System CX3; Beckman, Palo Alto, California, USA). Polyethylene glycol was determined by the method of Hyden.¹⁴ Absorption rates were calculated from the perfusion rate and the changes in polyethylene glycol and electrolyte concentrations in the test segment as previously reported.¹⁵

STATISTICAL ANALYSIS

Results are expressed as mean (SEM). For statistical analysis, unpaired two tailed Student's *t* tests were performed. *p* < 0.05 was considered significant. A linear least squares regression analysis was performed to determine the difference in absorption/secretion between the control period and the test period.

Table 1 Effect of capsaicin infusion (10 µg/ml) on jejunal absorption of water and electrolytes from plasma-like electrolyte solution

	Initial control	Capsaicin infusion	Final control
Net water movement (ml/30 cm/h)	-192 (11)	-201 (8)	-181 (7)
Sodium (mEq/30 cm/h)	-24.2 (1.6)	-26.1 (1.1)	-22.2 (1.0)
Potassium (mEq/30 cm/h)	-1.1 (0.06)	-1.1 (0.04)	-1.1 (0.04)
Chloride (mEq/30 cm/h)	-10.7 (1.1)	-13.1 (0.7)	-8.4 (0.7)
Bicarbonate (mEq/30 cm/h)	-11.5 (0.4)	-12.0 (0.3)	-11.6 (0.2)

Minus sign indicates net absorption. Values are mean (SEM) for eight subjects.

Figure 2 Absorption of water during the initial control period and during the test period for all capsaicin doses for each subject.

Results

Infusions of the control solution and the solutions containing 5 and 10 µg/ml capsaicin were generally well tolerated. Two volunteers receiving 10 µg/ml developed abdominal cramps at the end of the 60 minute test period. Cramps resolved within five minutes of the end of the capsaicin perfusion according to the protocol. When 50 µg/ml capsaicin was infused, the volunteer developed crampy abdominal pain within 20 minutes and pain persisted until the end of the 60 minute test period. Therefore no further studies were performed with this high capsaicin concentration. Cramps or abdominal discomfort did not develop during any of the control periods.

Table 1 shows that there were no changes in the rates of jejunal absorption of water, sodium, potassium, chloride, and bicarbonate during or after perfusion of 10 µg/ml capsaicin. Capsaicin at a concentration of 5 µg/ml also failed to affect jejunal absorption. Figure 2 shows individual data of absorption of water during the initial control period and during the test period for all capsaicin concentrations used. Individual changes in electrolyte absorption paralleled the changes in water movement (data not shown). Absorption values in the one subject in whom 50 µg/ml capsaicin was used were within the range of observations obtained with 10 µg/ml capsaicin.

To assess whether short term effects of capsaicin on absorption were missed by pooling the three 20 minute collections, we separately analysed the three 20 minute samples obtained during each of the capsaicin test periods. Electrolyte and water absorption in the first and third 20 minute collection period were not significantly different.

Discussion

The aim of the current study was to examine fluid and electrolyte transport after afferent neurons in the jejunum of healthy volunteers had been stimulated by topically applied capsaicin. With an in vivo infusion technique that has been validated for the assessment of absorption and secretion in humans in vivo,¹⁵⁻¹⁸ we failed to show any changes in electrolyte and water absorption by capsaicin. Thus in our model we were not able to extend the observations made in experimental animals to the human jejunum. It follows that, unlike in the guinea pig⁷ and rat^{9,10} gut, capsaicin sensitive nerves in the human intestine¹⁹ do not contribute to the physiological regulation of net absorption and secretion.

Although theoretically possible, we do not think that effects of capsaicin on mucosal function were missed as a consequence of the study design. Two points argue against the hypothetical possibility that the concentrations of capsaicin used in our study were too low to have an effect in human jejunum. Firstly, the capsaicin concentrations used in our study (5–50 µg/ml = 16–160 µM) were within the range of concentrations (10–160 µM) that caused sensory nerve mediated vasodilation in the rat stomach.¹⁹ Secondly, the concentration of 50 µg/ml capsaicin, and, in two volunteers, 10 µg/ml, caused a painful crampy sensation in the abdomen. Owing to the pain that 50 µg/ml capsaicin caused in one volunteer, further study of this and higher concentrations of the drug was not possible. It can be excluded that the pain was due to the volume effect of the infusion or intestinal distension by the occluding balloon since pain did not develop during the control periods preceding and following the capsaicin infusions.

Since comparison of the first 20 minute collection obtained during the capsaicin test period with the third 20 minute collection period did not show any differences in absorption, it is also unlikely that our study design missed any short lasting effects of capsaicin, given that the stimulant action of capsaicin on afferent neurons is rapidly desensitising.²⁰

It is concluded therefore that capsaicin does not affect net water and electrolyte movement in the human jejunum, which contrasts with previously reported findings in animals.^{7,9,10} Capsaicin sensitive afferent neurons are hence unlikely to participate in the physiological control of electrolyte and fluid transport in the human small intestine. It remains to be determined, however, whether these neurons come into play under the pathological conditions of hypersecretion caused by bacterial toxins, as has been shown in animal experiments.^{9,10}

Despite its ineffectiveness on secretion and absorption, intrajejunal capsaicin had a distinct action in that it caused abdominal discomfort and overt pain. This effect was concentration- and time-related, given that pain was felt only at the end of the capsaicin test period during two out of eight experiments with 10 µg/ml capsaicin but had already developed during the first third of the capsaicin test period and persisted until the end of the perfusion during the only experiment with 50 µg/ml capsaicin. The ability of intrajejunal capsaicin to give rise to pain was unexpected, since exposure of the rat gastric mucosa to 5-fold higher concentrations of capsaicin failed to evoke pseudoaffective reactions indicative of pain.²¹ On the other hand, the sensation of pain observed in the current study is consistent with the high algesic potency of capsaicin, which is due to its stimulant action on nociceptors.²⁰ It is not possible to infer from the present findings whether capsaicin caused pain by directly stimulating nociceptive afferents in the intestinal mucosa or by stimulating motility^{11,12} as might be deduced from the crampy nature of the sensation. Stimulation of motility may result in pain from excessive contractions or movement of the inflated balloon along the intestine. Excessive contraction or distension of the gut is well established to give rise to pain,²² whereas chemical nociception in the intestine has been little studied. Future studies will have to evaluate the mechanisms by which capsaicin causes pain in the human jejunum.

- 1 Grundy D, Scratcherd T. Sensory afferents from the gastrointestinal tract. In: Wood JD, ed. Schultz SG, section ed. *Handbook of physiology*; section 6: the gastrointestinal system. Bethesda: American Physiological Society, 1989:593–620.
- 2 Szolcsanyi J. Antidromic vasodilation and neurogenic inflammation. *Agents Actions* 1988;23:4–11.
- 3 Holzer P, Bartho L. Sensory neurons in the intestine. In: Geppetti P, Holzer P, eds. *Neurogenic inflammation*. Boca Raton: CRC Press, 1996:153–67.
- 4 Hubel KA. The effects of electrical field stimulation and tetrodotoxin on ion transport by the isolated rabbit ileum. *J Clin Invest* 1978;62:1039–47.
- 5 Cook HJ, Shonnard K, Highison G, et al. Effects of neurotransmitter release on mucosal transport in guinea pig ileum. *Am J Physiol* 1983;245:G745–50.
- 6 Cook HJ. Influence of enteric cholinergic neurons on mucosal transport in guinea pig ileum. *Am J Physiol* 1984;246:G263–7.
- 7 Vanner S, MacNaughton WK. Capsaicin sensitive afferent nerves activate submucosal secretomotor neurons in the guinea pig ileum. *Am J Physiol* 1995;269:G203–9.
- 8 Udupihille M. The effect of capsaicin on the small intestinal absorption of glucose and alanine in the rat. *Indian J Physiol Pharmacol* 1993;37:59–62.
- 9 Nzegwu HC, Levin RJ. Luminal capsaicin inhibits fluid secretion induced by enterotoxin E. coli STa, but not by carbachol, in vivo in rat small intestine and large intestine. *Exp Physiol* 1996;81:313–15.
- 10 Castagliuolo I, LaMont JT, Letourneau R, et al. Neuronal involvement in the intestinal effects of Clostridium difficile toxin A and Vibrio cholerae enterotoxin in rat ileum. *Gastroenterology* 1994;107:657–65.
- 11 Maggi CA, Patacchini R, Santicioli P, et al. Specific motor effects of capsaicin on human jejunum. *Eur J Pharmacol* 1988;149:393–5.
- 12 Maggi CA, Patacchini R, Santicioli P, et al. Human isolated small intestine: motor responses of the longitudinal muscle to field stimulation and exogenous neuropeptides. *Archives of Pharmacology* 1989;339:415–23.
- 13 Maggi CA, Patacchini R, Santicioli P, et al. Human isolated small intestine: motor responses of the circular muscle to field stimulation and exogenous neuropeptides. *Archives of Pharmacology* 1990;341:256–61.
- 14 Hyden SA. A turbidimetric method for the determination of higher polyethylene glycols in biological materials. *Annals of the Royal Agricultural College Sweden* 1956;22:139–45.
- 15 Petritsch W, Eherer AJ, Holzer-Petsche U, et al. Effect of cholera toxin on the human jejunum. *Gut* 1992;33:1174–8.

- 16 Fordtran JS, Rector FC, Carter NW. The mechanisms of sodium absorption in the human small intestine. *J Clin Invest* 1968;**47**:884–900.
- 17 Petritsch W, Holzer-Petsche U, Hinterleitner T, *et al.* Intravenous atrial natriuretic peptide does not affect water and ion transport in the human small intestine. *Eur J Clin Invest* 1989;**19**:272–7.
- 18 Reicht G, Petritsch W, Eherer AJ, *et al.* Absorption of hydrolysed bovine serum albumin from the human jejunum over a 6-hour period. *Eur J Gastroenterol Hepatol* 1997;**9**:81–5.
- 19 Holzer P, Lippe IT. Stimulation of afferent nerve endings by intragastric capsaicin protects against ethanol-induced damage of gastric mucosa. *Neuroscience* 1988;**27**:981–7.
- 20 Holzer P. Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacol Rev* 1991;**43**:143–201.
- 21 Holzer P, Livingston EH, Saria A, *et al.* Sensory neurons mediate protective vasodilation in rat gastric mucosa. *Am J Physiol* 1991;**260**:G363–70.
- 22 Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 1994;**107**:271–93.

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