Stimulation of β -adrenoceptors with isoprenaline inhibits small intestinal activity fronts and induces a postprandial-like motility pattern in humans

M Thollander, T H Svensson, P M Hellström

Abstract

Aims—To investigate the effects of β -adrenoceptor stimulation, using the agonist isoprenaline and the antagonist propranolol, on migrating motor complexes in the upper intestine of 16 healthy human volunteers.

Methods—Fasting motility was monitored using a tube with water perfused side holes connected to a pneumohydraulic system. Continuous eight hour recordings were obtained from each volunteer after a 12 hour fasting period. In all experiments, saline was given as control for the first four hour period and β -adrenergic agents for the next four hours. In separate control studies, saline was given for the whole eight hour period.

Results—Isoprenaline ($2.5 \mu\text{g/kg/min}$) reduced the number of activity fronts (phase III) of migrating motor complexes from 3 (2–4) in controls to 1 (0–2) during isoprenaline infusion ($p < 0.01$). Also, phase II-like activity replaced the regular motility pattern ($p < 0.01$). By contrast, propranolol ($25 \mu\text{g/kg/min}$) did not induce any significant changes in phase III compared with controls. Saline alone had no effect on motor activity.

Conclusions—Isoprenaline inhibited activity fronts in the human proximal small intestine and induced a postprandial-like motility pattern, whereas propranolol did not affect motor patterns. Stimulation of β -adrenoceptors is of importance in the control of motor activity of the human small intestine, especially under stressful conditions with high adrenergic activity.

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Keywords: isoprenaline, propranolol, migrating motor complex, small intestine.

The influence of adrenergic compounds on motility of the small intestine has been described in several investigations on different species. Stimulation of α_2 -adrenoceptors has been shown to inhibit intestinal motility in both animals^{1–4} and humans,^{5,6} whereas α_1 -adrenoceptors seem to be of minor importance in the control of gut motor activity.⁷ However, β -adrenergic stimulation has also been shown to play a part in the regulation of fasting motility. In a recent study, we showed that β -adrenoceptors regulate myoelectric activity in the small intestine of rats; stimulation of β_2 -adrenoceptors induces a postprandial-like motility pattern whereas

stimulation of β_3 -adrenoceptors inhibits myoelectric activity of the small intestine.⁸

In humans, β -adrenoceptor stimulation reduces oesophageal,⁹ antral,⁹ and duodenal motility.¹⁰ By contrast, β -adrenoceptor inhibition with propranolol was recently found to enhance motility of the oesophagus,¹¹ promote gastric emptying,¹² increase colonic intraluminal pressure,¹³ and shorten the period of postoperative adynamic ileus after bowel surgery.^{14,15}

As an extension of our previous studies on effects of β -adrenergic compounds on myoelectric activity in rats,⁸ we evaluated the effects of isoprenaline and propranolol on fasting duodenojejunal motor activity in healthy volunteers. To our knowledge, no studies have yet been performed to investigate the effects of β -adrenergic agents on the migrating motor complex in the small intestine of humans. Thus the purpose of this study was to explore the potential role of β -adrenoceptors in the control of fasting motility in the human small bowel.

Methods

Volunteers

Sixteen healthy male volunteers aged 21–55 (mean 32.0) years participated in the study. None reported symptoms or history of gastrointestinal disease and none was on medication. Seven of the subjects also participated in a control study in which only saline was given. The experimental protocol was approved by the local ethics committee at the Karolinska Hospital. Informed consent was obtained from all subjects.

Intestinal motility recordings

Motility of the proximal small intestine was monitored by means of a multichannel polyvinylchloride tube (William Cook, Bjaeverskov, Denmark). The tube was 250 cm in length and 4.7 mm in outer diameter and had seven channels 0.7 mm in width, ending as side holes at different levels. Four side holes, 10 cm apart, were used in this study. The tube assembly was passed through a nostril. Fluoroscopy was used to position the two proximal side holes in the descending (D1) and horizontal (D2) parts of the duodenum, and the distal two at the angle of Treitz (T) and in the jejunum (J). Each channel was continuously perfused with degassed water from a low compliance pneumohydraulic system (Arndorfer Medical Specialities, Greendale, WI, USA) at a rate of 0.4 ml/min. The channels were connected to external pressure transducers (PDCR 75, Druck Ltd,

Section of Gastroenterology, Department of Medicine, Karolinska Hospital, Stockholm, Sweden
M Thollander
P M Hellström

Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden
T H Svensson

Correspondence to:
Dr Per M Hellström, Section of Gastroenterology, Department of Medicine, Karolinska Hospital, S-171 76 Stockholm, Sweden.

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Leicestershire, UK). Recordings were made on a multichannel ink jet recorder (Mingograph 81, Elema-Schönander, Stockholm, Sweden). The velocity of the pressure rise on sudden occlusion of the recording system was 200 mm Hg/s in each channel.

Study design

The volunteers fasted overnight before the experiment. Recordings were started at 8 00–8 30 am and continued for eight hours. Volunteers were in recumbent position throughout the experiment. Each experiment consisted of two consecutive motility registration periods of four hours duration. A continuous infusion of saline was given during the first four hour control period and either saline, isoprenaline, or propranolol during the next four hours.

In the control group, comprising seven subjects, saline was given for two consecutive four hour periods. Isoprenaline (2.5 μ g/kg/min) was given to nine subjects and propranolol (25 μ g/kg/min) was given to seven volunteers.

Figure 1: Fasting motility of the small intestine in nine volunteers. Baseline represents phase I, $\square$ phase II, and $\blacksquare$ phase III (activity front) of migrating motor complex. Arrows indicate start and finish of continuous saline and isoprenaline (2.5 μ g/kg/min) during two four hour periods.

Blood pressure and heart rate were registered 10 minutes before drug administration and every 10 minutes thereafter. Subjects were monitored for side effects throughout the study.

Drugs

These were saline solution (9 mg/ml Natriumklorid, Kabi Vitrum, Stockholm, Sweden), isoprenaline (Apoteksbolaget, Umeå, Sweden) and propranolol (Zeneca, Macclesfield, Cheshire, UK).

Data analysis of migrating motor complex

Recordings were inspected by two independent observers who agreed on the presence or absence of motor patterns. Migrating motor complexes were identified according to criteria of Vantrappen *et al*¹⁶: (1) appearance of uninterrupted bursts of pressure waves with a frequency of 11–12 contractions per minute (phase III), (2) aboral migration of phase III activity passing at least the distal two registration points, and (3) a period of complete quiescence after phase III activity. Phase III of migrating motor complexes (activity front) was defined as the presence of uninterrupted phasic pressure changes for at least two minutes at the maximal frequency for that locus. The duration of phase III at each locus was measured from onset of regular contractions to quiescence. The propagation velocity of phase III was calculated by dividing the traversed distance from onset of phase III by the time interval from one registration point to the next. Phase II was defined as having ≥ 1 phasic contractions per minute, whereas phase I was defined as silence.

Statistics

Results are expressed as median values and range. Statistical comparisons with controls were made with Wilcoxon's signed rank test; $p < 0.05$ was considered significant.

Results

In every subject, each phase III of migrating motor complexes was observed migrating over all four intestinal recording sites.

In control studies with saline, the number of phase III migrating motor complexes recorded during the first four hour infusion period were 2 (2–4), compared with 2 (1–3) during the subsequent four hour recording period. Also, no changes were found for duration, contraction frequency, and propagation velocity of phase III between the two four hour periods.

Effects of β -adrenoceptor stimulation on migrating motor complex pattern

Isoprenaline decreased the number of phase III migrating motor complexes from 3 (2–4) in the control period to 1 (0–2) during isoprenaline infusion ($p < 0.01$; Fig 1). There were no changes in the duration, contraction frequency,

Characteristics of phase III of the migrating motor complexes in human volunteers during a four hour infusion of saline, followed by a four hour infusion of either isoprenaline (2.5 µg/kg/min; n=9), or propranolol (25 µg/kg/min; n=7)

		D1	D2	T	J
No of activity fronts	Sal	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)
	Iso	1 (0-2)**	1 (0-2)**	1 (0-2)**	1 (0-2)**
	Sal	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
	Prop	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)
Duration (min)	Sal	6.0 (3.9-6.2)	6.0 (4.7-6.6)	6.0 (4.6-8.5)	5.8 (4.9-7.4)
	Iso	5.4 (4.6-6.3)	5.7 (4.6-7.5)	5.9 (3.8-6.8)	5.7 (3.2-6.1)
	Sal	6.2 (4.4-8.8)	5.9 (4.3-8.1)	6.0 (3.3-6.3)	5.7 (3.2-6.4)
	Prop	5.7 (4.4-6.8)	6.0 (4.4-6.4)	6.1 (4.8-6.8)	6.6 (5.0-6.5)
Frequency (contractions/min)	Sal	11.1 (10.2-12.5)	11.2 (10.3-12.8)	11.4 (11.1-11.9)	11.4 (10.9-12.6)
	Iso	11.0 (10.0-11.5)	11.0 (10.0-11.9)	11.4 (10.6-12.4)	11.8 (11.2-12.3)
	Sal	11.2 (10.9-12.1)	11.8 (10.6-12.3)	11.1 (10.3-12.2)	12.0 (11.0-12.1)
	Prop	11.3 (11.0-12.0)	11.8 (10.7-12.3)	11.4 (10.5-11.9)	11.8 (11.1-12.2)
Velocity (cm/min)	Sal		12.5 (5.1-15.5)	8.9 (4.7-14.5)	9.4 (1.7-27.2)
	Iso		8.8 (3.8-19.3)	4.9 (4.1-15.0)	6.1 (4.1-11.0)
	Sal		17.9 (13.0-35.0)	12.8 (9.4-25.0)	11.0 (7.0-18.5)
	Prop		9.5 (4.6-37.5)	9.4 (6.0-19.3)	8.9 (4.7-14.5)

Results are expressed as median (range). D1 and D2 indicate positions of the side holes of the tube located 20 and 10 cm proximal to the angle of Treitz respectively. T and J indicate side holes at ligament of Treitz and 10 cm distal to the angle respectively. Sal=saline; Iso=isoprenaline; Prop=propranolol. **p<0.01.

and propagation velocity of phase III of migrating motor complexes compared with controls (Table). While suppressing the migrating motor complex pattern, isoprenaline induced phase II-like activity throughout the four hour infusion period. An increase in fraction of time occupied by this phase II-like activity was found (p<0.01), whereas decreases in phase I and III activity were registered (each p<0.01; Fig 2).

Isoprenaline increased systolic blood pressure from 120 (105-130) to 155 (130-165)

mm Hg (p<0.01), whereas the diastolic pressure decreased from 72 (70-90) to 40 (26-70) mm Hg (p<0.01). The heart rate increased from 60 (40-72) during the control period to 112 (100-135) beats/min during isoprenaline infusion (p<0.01).

Effects of β-adrenoceptor inhibition on migrating motor complex pattern

With propranolol at a dose of 25 µg/kg/min, the frequency of phase III did not change significantly (2 (1-3) during the control period and 2 (1-4) during propranolol infusion; Fig 3). No changes in duration, contraction frequency, or propagation velocity of phase III between the two four hour periods were found (Table).

The time fraction of the different phases of migrating motor complexes during propranolol infusion did not show any significant differences compared with the control period except for phase I (p<0.05; Fig 2).

Propranolol decreased systolic blood pressure from 120 (110-140) to 110 (100-130) mm Hg (p<0.05), whereas the diastolic pressure increased from 69 (55-80) to 80 (60-85) mm Hg (p<0.05). The heart rate decreased from 65 (60-79) during the control period to 51 (48-72) beats/min during propranolol infusion (p<0.05).

Discussion

Inhibitory sympathetic influence on gut motility was described as early as 1899 by Bayliss and Starling in their studies on the small intestine of dogs.¹⁷ Although the significance of this influence and its interaction with the parasympathetic nervous system was initially unclear, it soon became evident that extrinsic noradrenergic nerves play an important part in the regulation of gut motility.

The present study shows that non-selective β-adrenoceptor stimulation employing the agonist isoprenaline was associated with a reduction in phase III and an increase in phase II-like activity in the proximal small intestine of humans, whereas non-selective β-adrenoceptor inhibition using propranolol did not affect the basal migrating motor complex pattern. These findings are in accordance with several animal

Figure 2: Fraction of time occupied by phases I, II, and III. □ First four hour period when only saline was given; ■ second four hour period when (top panel) saline, (middle panel) isoprenaline, (bottom panel) propranolol was given. Fraction of the three phases is expressed as percentage of the respective four hour period. Values are given as medians. *p<0.05; **p<0.01.

Figure 3: Fasting motility of the small intestine in seven volunteers. Baseline represents phase I, $\square$ phase II, and $\blacksquare$ phase III (activity front) of migrating motor complex. Arrows indicate start and finish of continuous saline and propranolol (25 μ g/kg/min) during two four hour periods.

studies in which systemic administration of mixed β_1 -adrenoceptor and β_2 -adrenoceptor agonists exerted specific effects on intestinal motility.^{8 18 19} Depending on the gut segment studied, however, disparate motility effects have been reported.^{8 18-21}

The location of the β -adrenoceptors influencing gut motility is still controversial. According to most data, β -adrenoceptors are located on the smooth muscle cell^{22 23} where they increase binding of calcium to the cell membrane, which in turn has a stabilising effect on muscle cell activity.

It has been suggested that β_2 -adrenoceptors are located on the smooth muscle cells, mediating an inhibitory effect when stimulated.²¹⁻²⁴ β_1 -Adrenoceptors, on the other hand, are thought to exert an inhibitory influence on preganglionic or postganglionic cholinergic neurons,^{21 24 25} as well as exerting a direct inhibitory effect on smooth muscle cells.²¹⁻²⁴

Recent data suggest that β -adrenoceptor mechanisms may have a more important role in modulating intestinal motor function than α -adrenoceptors. Isoprenaline inhibits motor activity in the small intestine,^{25 26} whereas propranolol, under in vitro conditions, does not affect spontaneous motility.²⁷ However, propranolol abolished the inhibition of spontaneous motility induced by perivascular nerve stimulation,²⁷ which indicates that this sympathetic effect is mediated through β -adrenoceptor

stimulation. In the rabbit ileum, inhibition of sympathetically induced loss of contractility is abolished by the β_1 -adrenoceptor antagonist atenolol (75%) as well as by the β_2 -adrenoceptor antagonist butoxamine (25%). This is in agreement with the above mentioned hypothesis of both β_1 -adrenoceptor and β_2 -adrenoceptor responsiveness in smooth muscle cells.²⁸ In a recent study we showed that mainly β_2 -adrenoceptor stimulation is important in the regulation of motility of the small intestine in rats by disrupting the regular migrating motor complexes pattern and inducing irregular spiking.⁸ In the same species, stimulation of β_1 -adrenoceptors did not affect myoelectric activity. In addition, atypical β -adrenoceptors (for example, the β_3 subtype), which are distributed in the gastrointestinal tract^{29 30} disrupt the regular migrating motor complexes, and induce quiescence in rats when given intravenously.⁸ The importance of β_3 -adrenoceptor stimulation in the human gut is still of unknown biological relevance.

To date, few studies have investigated the effects of β -adrenergic compounds on motility of the small intestine in humans. In the study by McIntyre *et al.*,¹⁰ carried out in the post-prandial state, isoprenaline infusion delayed oro-caecal and duodenocaecal transit compared with placebo. This effect is likely to be due to an effect on motor function as isoprenaline was reported to reduce the amplitude of post-prandial antral contractions.¹⁰ Our present findings in fasted humans confirm that β -adrenoceptor stimulation in humans may influence motility of the small bowel by disrupting the regular migrating motor complex pattern. Our results and those of McIntyre *et al.*¹⁰ may initially seem contradictory, as our results showed increased contractile activity – that is, phase II-like activity – during the whole period of isoprenaline infusion. However, the occurrence of phase III decreased during isoprenaline infusion but no obvious effect was seen on the amplitude of duodenal or jejunal contractions. Taken together with the fact that phase III is the most important phase contributing to the propulsive capacity of the intestine, this may confirm its inhibitory action on motility expressed as decreased oro-caecal and duodenocaecal transit, confirming the findings of McIntyre *et al.*¹⁰ Of note, the dose of isoprenaline used in their study was one order of magnitude lower than the one used in the present study to achieve an effect on the fasting motor pattern. The differences in doses used may reflect differences in sensitivity of the small intestine to β -adrenoceptor stimulation under different motor patterns, such as postprandial and fasting motility.

By contrast with isoprenaline, propranolol has been shown to accelerate oro-caecal as well as duodenocaecal transit of both solid and liquid meals in humans.¹⁰ This effect is thought to be mediated by β_1 -adrenoceptors as atenolol produces a similar degree of acceleration of transit as propranolol. Similar to the findings of McIntyre *et al.*,¹⁰ Morris *et al.*³¹ found that isoprenaline reduced motor wave activity in humans, but propranolol had no consistent

motor effect. This is in accordance with results from a recent animal study, as well as with our present study, in which propranolol did not exert any consistent effect on fasting motor activity of the small intestine. These results may be explained by the fact that propranolol's effect on oro-caecal transit time is not mainly due to an action on small intestine, but rather on gastric emptying and colonic motility (see introduction). Thus the paucity of effect of β -adrenoceptor inhibition in this study suggests little physiological role for β -adrenoceptor mechanisms in the regulation of small intestinal motility. However, the stimulatory effect of non-selective β -adrenoceptor agonists producing phase II-like activity by disrupting the migrating motor complexes pattern favours a role for β -adrenoceptor stimulation during sympathetic activation of the gut as seen in stress reactions. Evidence for such mechanisms has been presented by Valori *et al.*³² In their study in humans, different kinds of stressors produced irregular contractile activity in the proximal small intestine, simultaneously with reduced frequency of phase III activity. These findings are commensurate with our present data from experiments on the small intestine in rat,⁸ as well as the current study in humans. The effects of β -adrenoceptor activation in this study closely resemble the initiation of a motor pattern after feeding. Thus the findings may display drug induced conversion of fasted state into a postprandial motility pattern.

The present results do not discriminate between β_1 -adrenoceptor and β_2 -adrenoceptor stimulation in the control of upper small intestinal motility in humans. However, earlier animal studies by our group⁸ suggest that β_2 -adrenoceptor stimulation preferentially induces irregular spiking activity and inhibits activity fronts similar to effects noted in humans. Further investigations to explore the relative importance of different subsets of adrenergic β_1 -receptors and β_2 -receptors for gut motility in humans are therefore needed.

Finally, as the dose of isoprenaline used in our study is within recommendations for clinical usage, central nervous effects of the drug would be minimal. In this study, no major side effects were noted by the subjects when isoprenaline or propranolol was given. The findings, therefore, indicate that β -adrenergic control of motor activity in human small intestine involves peripheral mechanisms. A possible clinical implication of these findings relates to the increasing use of pharmacological agents to ameliorate motility disorders of the gastrointestinal tract in humans.

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