Modulation of human upper intestinal nutrient transit by a beta adrenoreceptor mediated pathway

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Abstract

To explore the role played by beta adreno-receptor mediated pathways on human upper gut function a series of studies were conducted into the effects of beta adrenoreceptor agonists and antagonists on orocaecal and duodeno-caecal transit and on antral and duodenal motor activity. Under control conditions orocaecal transit was consistent within individuals (mean coefficient of variation (18·0%) but varied widely between individuals (median transit 63 minutes, range 33–164). Prior administration of the non-selective beta adrenergic antagonist propranolol consistently hastened orocaecal transit (median transit 51:25–93, *v* control p<0·005). The selective beta-1 antagonist, atenolol, also hastened transit (median transit 50:35–93 minutes, *v* control p<0·01). The magnitude of an individual's response to beta blockade correlated closely with the orocaecal transit (Tau=0·54, p<0·01). Duodenocaecal transit was also hastened by propranolol from control values of 66:45–107 minutes to 50:16–62 minutes, p<0·025). In contrast neither duo-denal nor antral motility were consistently altered by beta blockade. The beta adreno-receptor agonist, isoprenaline, delayed both orocaecal transient (97:55–178 minutes, *v* control p<0·005) and also duodenocaecal transit (160:45–215 minutes, *v* 73:40–133) (p<0·025). Isoprenaline also reduced antral motility by an effect which appeared to occur predominantly through a reduction in con-traction amplitude (from a median amplitude of 27: 5·39 mm Hg to 14: 3–24 mm Hg, p<0·03) rather than an effect on the interval between contractions. No effect on either amplitude or frequency of duodenal motor activity was observed. A beta adrenoreceptor mediated pathway thus appears to exert a biologically relevant effect on gut function not only under conditions of sympathetic stimulation, but also at rest when a basal beta adrenergic tone appears to influence the speed of nutrient transit through the human upper gut.

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The major effects of the sympathetic nervous system on the function of the human body have been well recognised since the time of Cannon.[1] Results of sympathetic pathway stimulation on the body may be classified according to responses to different catecholamines into alpha (pre-dominantly adrenaline responsive) and beta (predominantly adrenaline responsive). Beta receptors are further divisible into beta-1 and beta-2 subtypes.[2]

In man beta-1 mediated effects are usually recognised by changes in pulse rate and blood pressures wheras beta-2 specific actions induce bronchodilation and hypokalaemaia.[3]

Although the physiological responses to sympathetic stimulation are well known for some human organ systems – for example, the cardio-vascular system, responses in the human gut are less well defined. Sympathetic nervous activity has been recognised to influence motor function in the gut since Bayliss and Starling first showed inhibition of intestinal peristalsis in animals by electrical stimulation of the splanchnic nerves, and an increase in peristalsis when the nerves were divided.[4] The distribution of sympathetic fibres to the enteric nervous system[5] and the localisation of alpha adrenoreceptors on enteric nerves[6] indicate that sympathetic nerves release noradrenaline into myenteric axo-axonal synapses which, through post ganglionic alpha adrenoreceptor stimulation reduce cholinergic activity in enteric nerves.[7] In contrast, beta-adrenoreceptors do not appear to be localised on enteric nerves but have been found on gastro-intestinal smooth muscle.[8] In vitro, beta agonists inhibit contraction of isolated smooth muscle cells[8] and electrically stimulated muscle strips[9] whilst beta antagonists enhance contraction.

Beta adrenergic influences on intact human gastric function have been identified by Rees *et al* who showed that the beta agonist isoprenaline delayed, while the beta antagonist propranolol accelerated gastric emptying.[10] Further evidence for beta adrenoreceptor modulation of human upper gut function has recently been provided in experiments showing that experimental sym-pathetic stimulation by hand immersion in cold water delays orocaecal transit, an effect which is attenuated by prior administration of beta adrenoreceptor antagonist drugs.[11]

The aim of the current series of studies was to extend the understanding of beta adrenoreceptor mediated effects on human upper gastro-intestinal motor function by administering beta adrenoreceptor agonists and antagonists to normal individuals.

Three groups of studies were conducted in the following sequence. The first examined the effect of these agents on orocaecal transit time. The second group studied effects on duodeno-caecal transit to determine whether the effects observed in the first group extended beyond the stomach. The third group of studies investigated the effects of adrenoreceptor stimulation on antral and duodenal motor activity to determine whether beta-adrenoreceptor mediated effects on transit could be exerted through an action on gastric or duodenal motor patterns. The rationale for the motility experiments was based on reports that antral motility was inhibited by experimental sympathetic stimulation, an effect
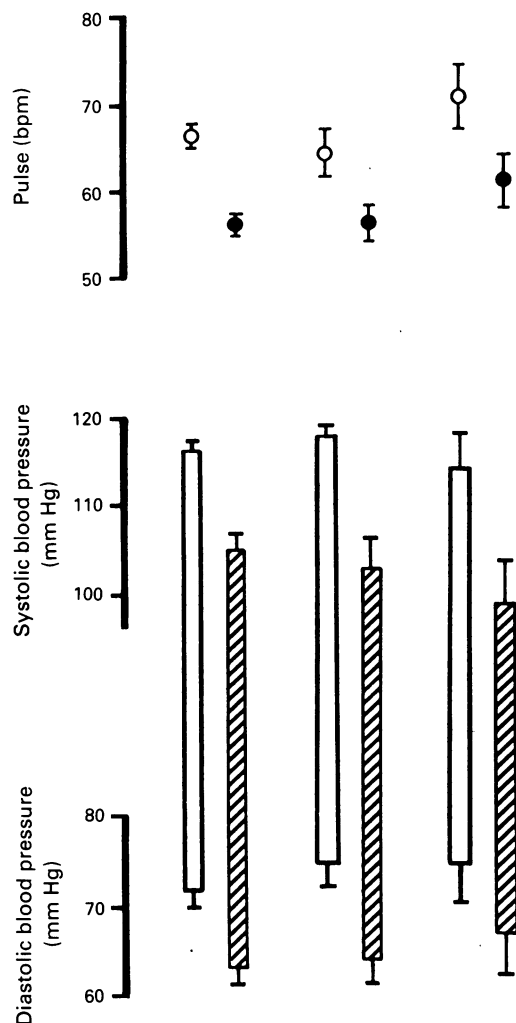
Figure 1: Cardiovascular parameters recorded during experiments number 2, 4, and 9 respectively are presented for the control studies (open circles and bars) and for the beta-antagonist studies (closed circles and hatched bars). Values represent mean and standard error.

which was attenuated by prior adrenoreceptor blockade[11][12] while studies of beta blockade alone on motility had shown no effect.[11]

Methods

VOLUNTEERS

All studies were conducted on healthy volunteers (age 19–34 years), drawn from medical and paramedical staff. None gave a current or past history of gastrointestinal disorder and all were accustomed to the environment of the clinical research laboratory, having performed transit studies on previous occasions. Protocols of all the studies were submitted to, and approved by, the local Ethnics Committee and all the volunteers gave written informed consent before participation.

PHARMACOLOGICAL AGENTS

All the drugs used for the experiments were commercially available preparations. Propranolol (Inderal, ICI plc) was used as a non-selective beta antagonist, and was administered orally in doses ranging from 40 to 160 mg one

hour before ingestion of the test meal, this time interval having previously been found to allow development of optimal betablockade.[11][13]

Atenolol (Tenormin 100 mg, Stuart Pharmaceuticals Ltd) was chosen for its beta-1 selective peripheral antagonist actions and was again administered orally one hour before test meal ingestion. When used to abolish the beta-1 agonist effects of isoprenaline, however, atenolol was given intravenously as a 5 mg loading dose followed by a 0·1 mg per minute intravenous infusion.

Isoprenaline (Saventrine, Pharmax Ltd), a non-selective beta agonist[14] was given at doses ranging between 0·005 to 0·06 µg/kg/min by intravenous infusion. In pilot studies the beta agonist action on cardiovascular parameters was found to reach a maximum effect after 10 minutes. Infusions were thus started at least 10 minutes before ingestion of the test meal in each transit study and 10 minutes before commencement of observations in motility studies.

Salbutamol (Ventolin, Allan & Hansburys, Ltd) a beta-2 selective agonist[14] was administered intravenously at a dose of 0·07 mg/kg/min. This dose was chosen on the basis of previously reported studies which indicated it to have optimal beta-2 adrenergic agonist activity (hypokalaemia) with minimal beta-1 agonist activity.[3]

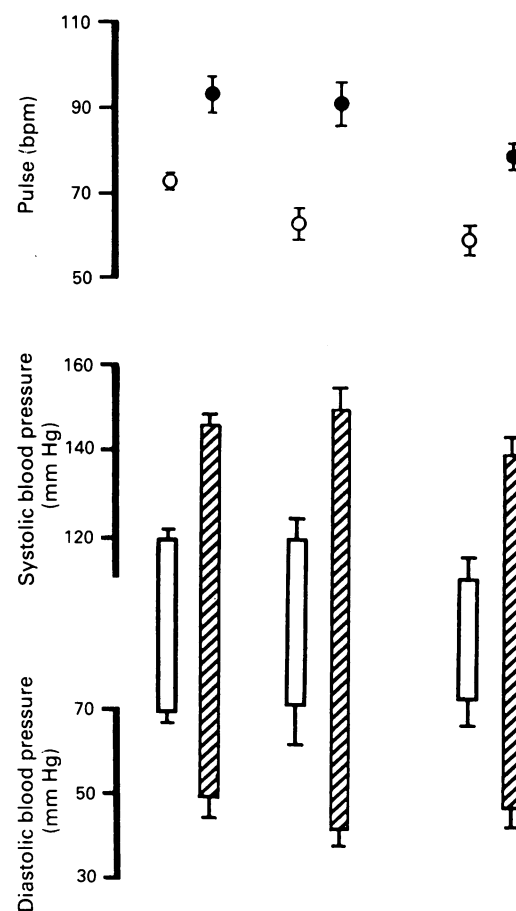For control experiments matching dummy tablets were supplied by the hospital

Figure 2: Cardiovascular parameters recorded during experiments number 6, 9, and 10 respectively are presented as in Figure 1 for the control studies (open circles and bars) and with isoprenaline (closed circles and hatched bars).
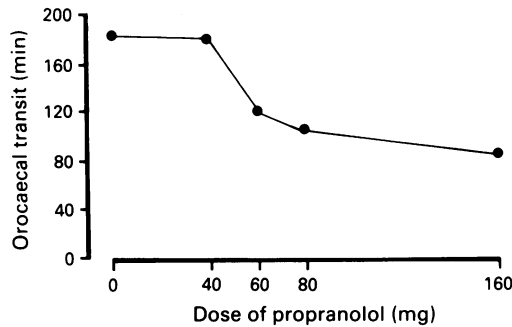
Figure 3: Relationship between orocaecal transit time and dose of propranolol in one subject.

Sum of orocaecal transit (control − propranolol) (min)

Figure 5: Plot of the sum of, and the difference in, orocaecal transit time for control and propranolol data indicating the change in interindividual variation under the two conditions.

pharmacy and normal saline was used for intravenous infusion.

EXTRA INTESTINAL MEASUREMENTS OF DRUG ACTIVITY

To provide a measure of the bioactivity of the drug in each study, effects on the cardiovascular system were monitored by serial measurements of radial pulse rate (beats/minute) and brachial artery blood pressure (by sphygmomanometer). The beta-2 agonist activity of salbutamol was measured by assaying serum potassium at 15 minute intervals.

OROCAECAL TRANSIT STUDIES

Orocaecal transit was determined using a previously validated and standardised breath hydrogen method.[15] The test meal consisted of 425 g chicken soup (H J Heinz Ltd) to which 20 g lactulose (Duphalac, Duphar Ltd) was added as a transient marker. The meal had a total osmolarity of 777 mOsmol, and contained 5·6 g protein and 11·4 g fat. Transit was measured as the interval between ingestion of the meal and the onset of a persistent rise in end expiratory breath hydrogen which at least doubled basal values. Subjects were studied after a 15 hour

overnight fast which followed an evening meal low in poorly absorbed carbohydrate to ensure that basal breath hydrogen at the onset of the study was less than 20 parts per million. Activities likely to affect breath hydrogen production were avoided during the experiments,[16] all of which were conducted in a quiet room with subjects in a semi-reclined position.

BETA ADRENORECEPTOR ANTAGONIST STUDIES

Experiment 1: Pilot study of the effect of propranolol on orocaecal transit

One subject performed repeated transit studies after ingestion of 40 mg, 60 mg, 80 mg, and 160 mg of propranolol on different occasions. The same individual then undertook six additional studies comparing the effect of propranolol (160 mg) with placebo, the order of the experiments being randomised.

Experiment 2: Single blind controlled study of propranolol on orocaecal transit

Based on the data obtained from the pilot study, the effect of propranolol (160 mg) on orocaecal transit time was compared with placebo in 21 volunteers (age 19–34 years; 17 men) using a single blind randomised order design.
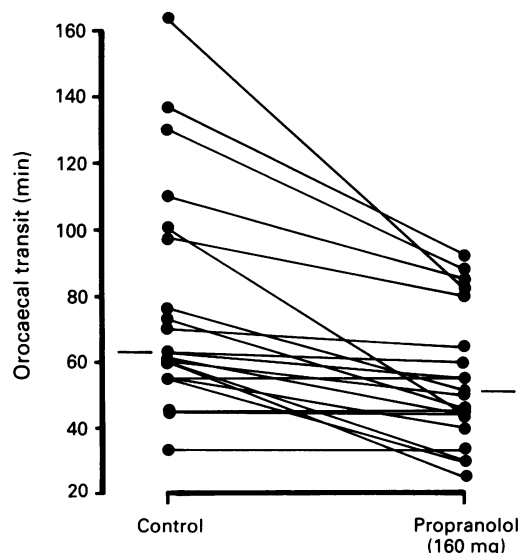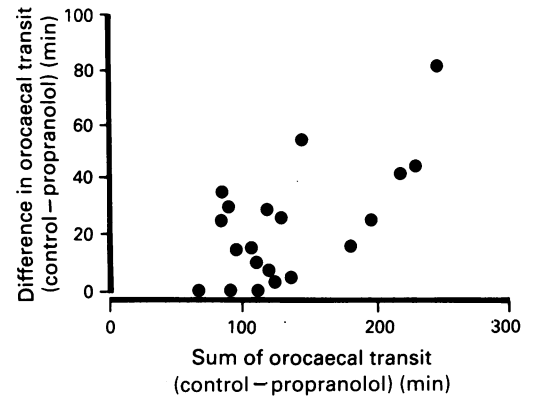

Figure 4: Orocaecal transit times for 21 subjects under control conditions and after propranolol 160 mg (median values are shown by the horizontal bars).
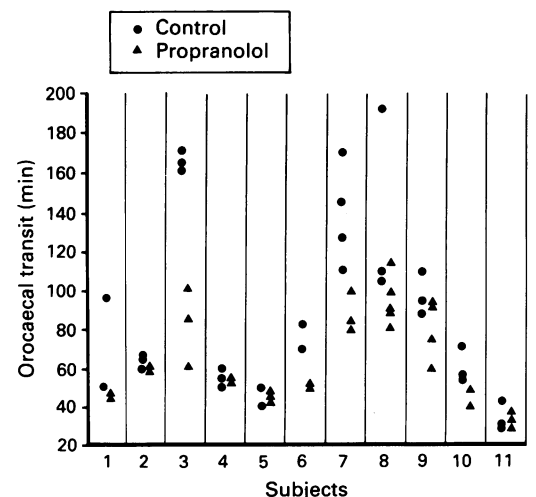

Figure 6: Results of the repeat studies on the 11 subjects are shown under control and propranolol pretreated conditions.
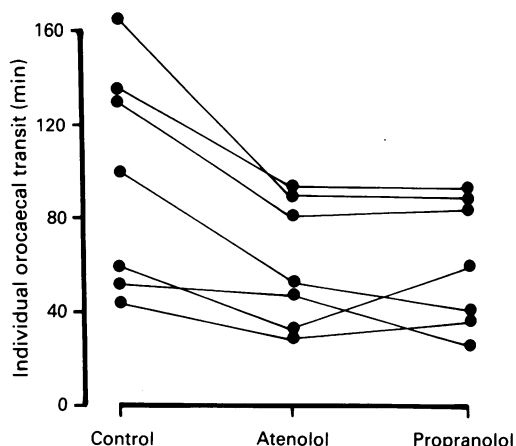
Figure 7: Individual orocaecal transit times in seven individuals under either control conditions or beta adrenergic blockade with either propranolol (beta 1 and 2 antagonist) or atenolol (a selective beta 1 antagonist).

Figure 9: Orocaecal transit time for 19 subjects under control conditions and during isoprenaline infusion (horizontal bars indicate median values).

Experiment 3: Repeatability studies

Eleven of the subjects who performed experiment 2 ingested 160 mg propranolol or placebo on two to five occasions each, in randomised order, following an identical protocol to experiment 2 to determine the degree of intraindividual variation of the response.

Experiment 4: Effect of atenolol on orocaecal transit

To investigate the beta adrenoreceptor subtype involved in control of orocaecal transit, seven of the subjects who particpated in the propranolol study (experiment 2) repeated the protocol using the more beta-1 specific antagonist atenolol.

BETA ADRENORECEPTOR AGONIST STUDIES

Experiment 5: Pilot study of the effect of isoprenaline on orocaecal transit

Seven studies were performed in one individual using isoprenaline at doses of 0·005, 0·015, 0·03 and 0·06 µg/kg/min to construct a dose response curve. The same subject then underwent six further studies comparing 0·015 µg/kg/min with saline in randomised order.
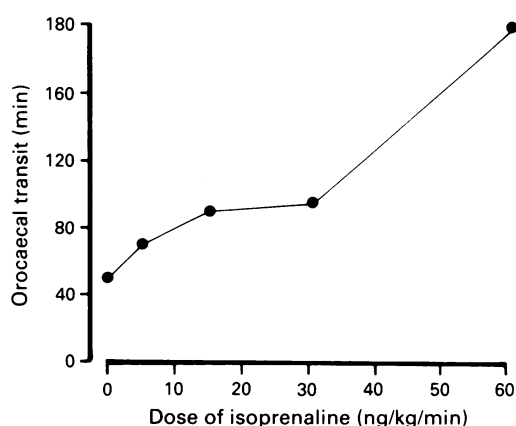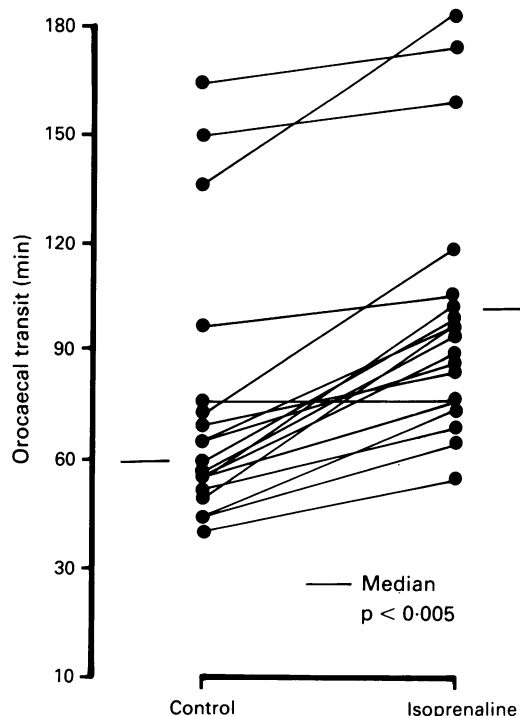
Experiment 6: Single blind controlled study of isoprenaline on orocaecal transit

Isoprenaline 0·015 µg/kg/min was compared with saline infusion in 19 volunteers (age 19–33 years; 16 men) in a single blind randomised order study. This dose was selected because it produced a marked change in transit in the pilot study without major changes in cardiovascular variables. A previous study had also shown this dose to be capable of altering fluid and electrolyte movement across the gastrointestinal mucosa.[17]

Experiment 7: Repeatability studies

Eight subjects who had participated in experiment 6 repeated both the isoprenaline and saline infusion studies on two to four occasions in randomised order to assess the repeatability of the isoprenaline effect.

Experiment 8: Studies on the adrenoreceptor subtype involved in the adrenoreceptor agonist effect

(a) Effect of atenolol on isoprenaline induced orocaecal transit delay

To determine whether the beta-1 selective antagonist atenolol would abolish any delaying effect of isoprenaline on orocaecal transit, two of the subjects who had participated in experiment 6 received an infusion of the drug together with either intravenous atenolol, or saline in a single blind randomised order study.

(b) Effect of salbutamol on orocaecal transit

To further investigate the role of beta adrenoreceptor subtypes in the agonist effect salbutamol, a more selective beta-2 agonist was administered intravenously to the same two

Figure 8: Relationship between orocaecal transit time and dose of isoprenaline. Symbols represent individual values in one individual.

subjects who participated in experiment 8a, using a similar protocol to that for experiment 6.

DUODENOCAECAL TRANSIT STUDIES

Before each study, all subjects were prepared in an identical manner to the orocaecal transit experiments. On arrival in the study unit, a fine bore feeding tube (external diameter 2 mm) was swallowed and positioned with the aid of fluoroscopic imaging so that its tip was in the second part of the duodenum. Transit was defined as the interval between time of administration of 100 ml of an isoosmolar lactulose test solution (delivery slowly into the duodenum over three minutes to minimise intraluminal distension) to the onset of a sustained breath hydrogen rise.

Experiment 9: Single blind controlled studies of propranolol or isoprenaline on duodenocaecal transit
These studies were designed to explore the effect of beta antagonists and agonists on small intestinal transit. The effect of propranolol was compared with placebo in six subjects, while in six further subjects the effect of an isoprenaline infusion was compared with saline infusion.

ANTRODUODENAL MOTILITY STUDIES

Volunteers attended the laboratory after a preparation identical to that used for the orocaecal transit studies. Each swallowed a multilumen manometry tube which was positioned fluoroscopically so that two distal ports lay in the second and third part of the duodenum, while eight further ports, situated at 1 cm intervals, lay on either side of the pylorus. Positioning of the juxtapyloric ports was aided by the tube design which had a central radio opaque channel and radio opaque markers beside each port. After the identification of the irregular motor pattern characterising phase II

Figure 10: Repeat studies on eight subjects are shown both under control conditions and during isoprenaline infusion.

activity, subjects ingested a standard meal to induce postprandial motor activity. The meal was ingested over a 10 minute period and the tube adjusted if necessary over the subsequent three minutes to establish optimum recording conditions. Drug infusions were then started and after a further 10 minutes manometric activity was collected for analysis for a 15 minute period.

For detection of antral and duodenal motility patterns, each lumen was continuously perfused pneumohydraulically and connected to a strain gauge transducer (Gaeltec Ltd, Dunvegan, Skye, Scotland), its output then being fed into a chart recorder (Wanatabe Linearcorder Mark VII, Tokyo, Japan) to provide a permanent record.

Each individual performed two studies per study day to minimise radiation exposure. The second study was always started at least three hours after ingestion of the first meal, after the recurrence of a phase III pattern, characteristic of fasting motor activity and, after the return of cardiovascular variables to the basal state.

Experimental 10: Effect of isoprenaline on antroduodenal motility
The effect of isoprenaline on antroduodenal motility was compared with saline infusion in a single blind randomised order experiment. Each infusion started three minutes after ingestion of the meal and was given for 10 minutes before the observation period and for the duration of the 15 minute study period (giving a total infusion duration of 25 minutes).

DATA ANALYSIS

Cardiovascular data
The effect of beta agonists and antagonists on pulse and blood pressure were compared with control values using Student's paired t test[18] and are reported as mean and standard error of the mean.

Transit data
In the studies of orocaecal and duodenocaecal transit, the effect of the active drug was compared with placebo using Wilcoxon's paired sign rank test or Pratt's sign test (if $n<7$).[19] Because the measured variable may not be normally distributed results are reported as median and range. Correlations were determined using Kendall's rank correlation coefficient (Tau).[19]

The reproducibility of the test in each individual was calculated as the coefficient of variation, and reproducibility in the group is presented as the mean coefficient of variation.[18]

Antroduodenal motility data
Contractions were defined as those intraluminal pressure changes which could be distinguished from the respiratory artefact, excluding those which occurred synchronously in several channels and which could have been extraintestinal in origin. Antral activity was analysed from the most distal of the antral ports which
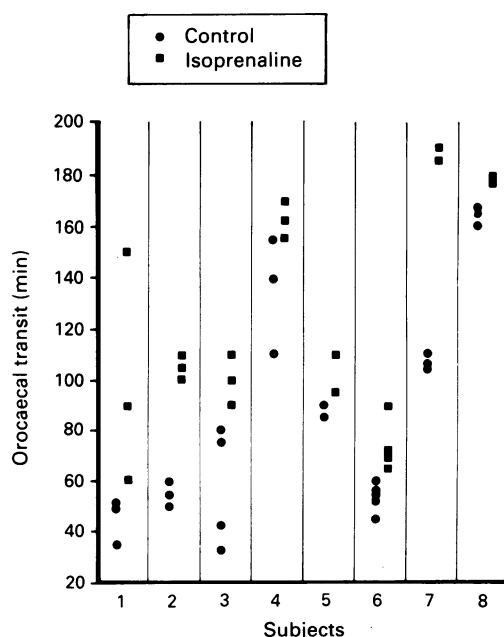
provided evaluable data during the study. Duodenal activity was obtained from the most distal channel sited in the second part of the duodenum.

Motor activity was analysed for a 15 minute period, beginning 13 minutes after completion of meal ingestion to ensure a consistent feeding pattern. The variables chosen for analysis were, the mean amplitude of intraluminal pressure activity (mm Hg) and the intercontraction interval (seconds). The differences between test and control values were compared using Pratt's sign test.[19]

Results

EXTRAINTESTINAL EFFECTS OF BETA AGONISTS AND BETA ANTAGONISTS

Propranolol and atenolol produced the expected reduction in pulse rate, systolic blood pressure and diastolic blood pressure in all individuals studied (Fig 1). No side effects were observed in any subjects in the beta antagonist studies. Isoprenaline increased the pulse rate, raised systolic, and reduced diastolic, blood pressure in each of the studies (Fig 2). Subjects were aware of mild palpitations during all but the lowest dose of isoprenaline. As expected, coadministration of atenolol completely abolished the cardiovascular changes produced by isoprenaline. Salbutamol reduced the serum potassium (mean change 0·36 mmol/l SEM=0·09, p<0·01) showing beta-2 agonist activity, but the cardiovascular parameters also changed, with a rise in systolic blood pressure (mean rise 13 mm Hg) suggesting concomitant beta-1 agonist effects at the dose used.

BETA ADRENORECEPTOR ANTAGONIST EFFECTS ON OROCAECAL TRANSIT

In the pilot study (experiment 1) propranolol consistently hastened transit compared with control values, the response being dose related (Fig 3).

The results of experiment 2 showed a wide interindividual difference in control orocaecal transit time values ranging from 30–164 minutes (Fig 4). Propranolol hastened orocaecal transit compared with the control studies (from 63:30–164 to 51:25–93 minutes, p<0·005). The acceleration induced by propranolol was greatest in those subjects with the longest orocaecal transit times, a direct correlation being found between control transit and degree of acceleration Tau=0·58, p<0·01).

Unfortunately, it is not possible to determine with any certainty what proportion of interindividual variation is dependent on the beta adrenoreceptor mediated pathway by comparing the difference in slope of the regression line with the line of intent because the error in control transit measurement will contribute an unknown reduction in the gradient. The extent to which variation in beta adrenoreceptor blockade induced acceleration, and hence might contribute to interindividual variability, can however be calculated by the method described by Bland.[20] This consists of first showing a significant change

in variation between control and test conditions, and second using the proportion of the variances as a measure of the beta adrenergic contribution. The relationship of the difference between and the sum of the test and control values was determined for all individuals. There was a good correlation between the control test value difference, and the sum of the two values for an individual (r=0·67) indicating a significant change in variance (p<0·001) (Fig 5). The contribution of the beta adrenergic component to interindividual variation was calculated from the ratio of the variances (418/1148) and indicated that 36% of the interindividual differences could be attributed to the variable activity of the beta adrenoreceptor mediated pathway.

The results of the repeat studies (experiment 3) show that administration of propranolol was consistently associated with reduction in transit (Fig 6). Intraindividual variation also fell slightly with transit acceleration, the mean coefficient of variation falling from 18% (SEM 4%) to 10% (SEM 2·7%).

Administration of atenolol (experiment 4) also hastened orocaecal transit from a median value of 100: (range 45–164) minutes to 50: (range 35–93) minutes, p<0·01. This hastening was similar in magnitude to that induced by propranolol (45:30–93 minutes) (Fig 7), the mean difference between the degree of acceleration produced by the two drugs being 1·47 minutes.

BETA ADRENORECEPTOR AGONIST EFFECTS ON OROCAECAL TRANSIT

In the pilot study (experiment 5) Isoprenaline consistently delayed orocaecal transit, the magnitude of the delay increasing with dose administration (Fig 8).

In the group study (experiment 6) isoprenaline 0·015 µg/kg/min consistently delayed orocaecal
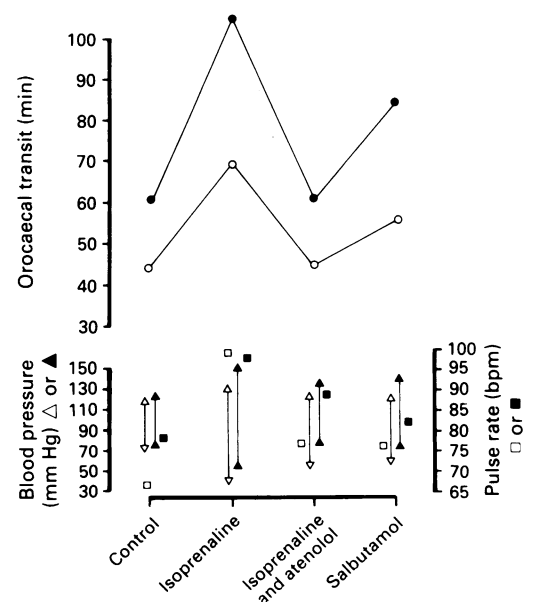

Figure 11: Mean orocaecal transit times and cardiovascular changes are shown in two individuals (subject 1=open symbols, subject 2=closed symbols) during control and beta agonist studies to show attenuation of the isoprenaline effect by atenolol and also the non-specific beta agonist effect of salbutamol at the dose used.
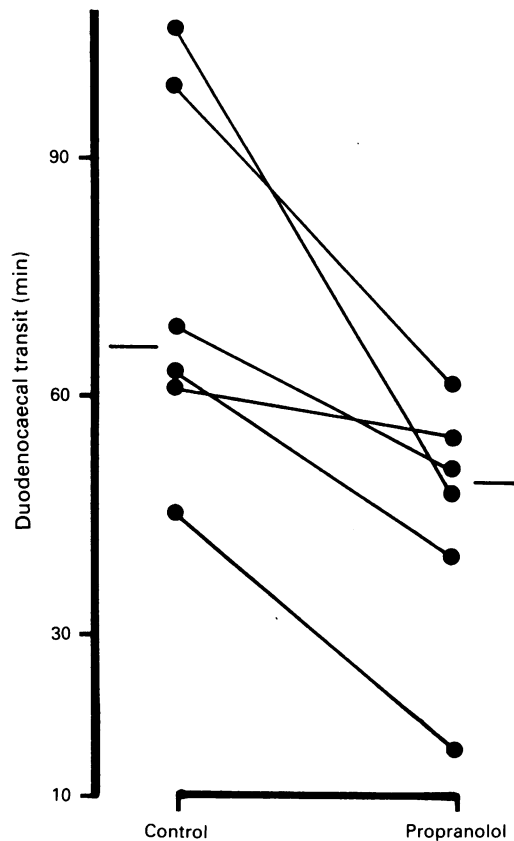
Figure 12: Accelerating effect of propranolol on duodenocaecal transit time (median values shown by horizontal bars).

Figure 13: Delaying effect of isoprenaline on duodenocaecal transit time (median values shown by horizontal bar).

transit, the rate during test infusion being slowed to 97 (range 55–178 minutes compared with the control values of 58 (40–165) minutes, p<0·01 (Fig 9).

Unlike the beta antagonists study, however, no relationship was found between the magnitude of the drug effect and orocaecal transit (Tau=0·09, p>0·1).

The isoprenaline induced transit delay was consistently reproduced in all the subjects when the study was repeated (experiment 7) (Fig 10).

Concomitant administration of atenolol and isoprenaline (experiment 8a) completely abolished the isoprenaline induced transit delay (control 45, 61 minutes: isoprenaline, 70, 105 minutes: isoprenaline+atenolol 45, 62 minutes), indicating that the isoprenaline effect was mediated by a beta-1 adrenoreceptor pathway (Fig 11).

Infusion of the beta-2 argonist salbutamol (experiment 8b) did delay orocaecal transit (control 45, 61 minutes, salbutamol 59, 92 minutes) (Fig 11). Concomitant rise of systolic blood pressure during infusion, however, indicated that beta-1 agonist activity was also present, and it was therefore not possible to exclude the possibility that the changes in orocaecal transit observed were related to the drugs beta-1 agonist effect.

DUODENOCAECAL TRANSIT STUDIES

Propranolol consistently hastened duodeno-caecal transit from 66:45–107 minutes under control conditions to 49·5:16·62 minutes after
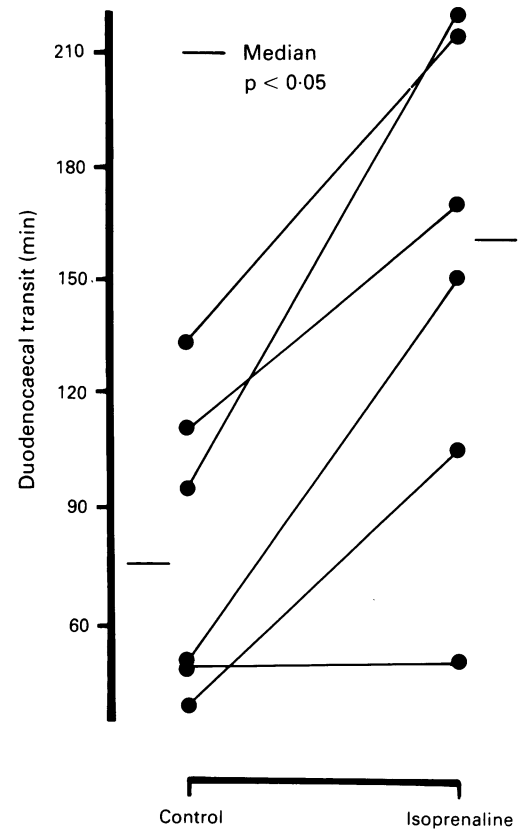
propranolol (p<0·025) (experiment 9) (Fig 12).

Isoprenaline consistently delayed duodeno-caecal transit from 72·5:40–133 minutes to 160:45–215 minutes (p<0·025) (Fig 13).

ANTRODUODENAL MOTILITY STUDIES

Isoprenaline reduced the mean amplitude of antral contractions from control values of 27 mm Hg (range 5–39) to 14 mm Hg (range 3–24), p<0·03 (experiment 10) (Fig 14). In contrast the interval between successive antral pressure waves was unchanged by isoprenaline (control intercontraction interval 19 seconds (range 7–142) v 19 seconds (range 7–336) (Fig 15). In the duodenum, no evidence was found to suggest that isoprenaline affected either intercontraction interval (control 17 (range 10–20 seconds) v isoprenaline 17 (range 11–39 seconds), p>0·05)) or amplitude, control 10 (range 7–19) v isoprenaline 10 (range 5–5) mm Hg (Fig 14).

Discussion
In his classical study of the differential responses of mammalian tissue to various adrenoreceptor agonists, Ahlquist designated receptors in the gut to the alpha subtype,[21] although with the advent of a selective beta adrenergic agonist he subsequently also showed the presence of beta adrenoreceptors.[22] In man, muscle strips from the stomach and the small intestine have been shown to possess beta adrenoreceptors which act in such a way that beta agonists relax, whilst beta antagonists enhance, muscle contraction.[9] Similar results have also be obtained using
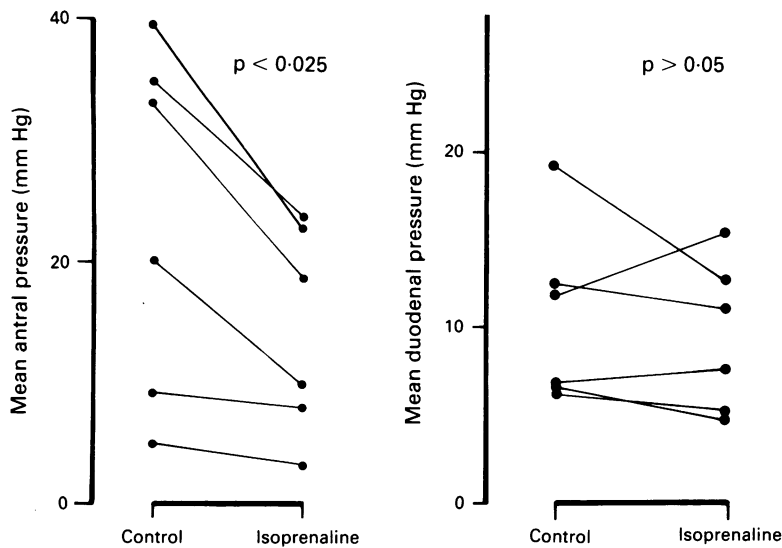
Figure 14: Effect of isoprenaline on antral and duodenal pressure is shown in six subjects.

isolated smooth muscle cells from the gastrointestinal tract indicating the presence of adrenoreceptors on smooth muscle.[23]

Alpha adrenoreceptors appear to inhibit gut motor function by attenuating cholinergic and serotonergic myenteric neural activity through axo axonal synapses.[24] In contrast, beta adrenoreceptors do not appear to be present in the myenteric plexus.[25] Sympathetic neural stimulation thus appears to inhibit gut motor activity through an alpha adrenoreceptor mediated pathway, which reduces enteric neuronally mediated excitation and through beta adrenoreceptors which appear to act directly on smooth muscle. Although there are relatively few sympathetic nerves which terminate in smooth muscle, clearance mechanisms to abolish the transmitter function of released noradrenaline appear relatively inefficient in the gut[26] so that diffusion of neurotransmitter outside the immediate vicinity of the synapse is likely to

permit smooth muscle beta receptor activation.

Our demonstration of a hastening of orocaecal transit by beta adrenoreceptor antagonists indicates the presence of a tonically active inhibitory beta adrenoreceptor mediated pathway in man. This observation is consistent with animal studies involving splanchnic nerve section[4][27] or guanethidine induced adrenergic neuronal blockade[28] which have also suggested the presence of a tonic sympathetic neural inhibition of motility. The fact that subjects with longer transit accelerate more than those with rapid transit after beta blockade and that the normally wide interindividual variation in orocaecal transit is greatly reduced suggests furthermore that the beta adrenoreceptor mediated inhibitory influence on transit is expressed to differing degrees by different individuals, while the similarity of the response in each individual indicates that the magnitude of this inhibition is consistently expressed.

The finding that isoprenaline delays orocaecal transit is again consistent with previous animal studies where splanchnic nerve stimulation has been shown to inhibit motor activity.[4] In addition, human studies using experimental stressors known to activate sympathetic pathways similarly delay orocaecal transit,[11] an effect which can be attenuated by previous beta blockade. Unlike the adrenoreceptor antagonist studies, however, the magnitude of response to isoprenaline did not appear to be related to unstimulated transit rate. The most likely reason for this appears to be that the dose of isoprenaline, used in the study was too low for the effect to be demonstrated. While it is possible to obtain virtually total beta-blockade in man without hazard, pharmacological beta adrenoreceptor stimulation is limited by untoward cardiovascular effects.[14] At the relatively low dose used in our studies we may not have provided sufficient stimulation to disclose interindividual variation in response. This suggestion is supported by our inability to reach a plateau phase in our isoprenaline transit dose response study before side effects developed.

The exact anatomical site or sites of action of the beta receptors which are modulating the transit effects is difficult to identify from the current data. Previous studies have shown effects on gastric function with acceleration of emptying during beta blockade and retardation by isoprenaline.[10] Our duodenocaecal transit studies which show a similar pattern of response to those exerted on the stomach suggest that the effects may be exerted throughout the small intestine as well as the stomach. Unfortunately, because of the necessary difference in meal constituents and experimental method it is not possible to directly compare the results of the orocaecal transit data with the duodenocaecal transit data and so the relationship between the two parameters or the relative size of the effect at the gastric or small intestinal level remains uncertain.

It is possible, however, that the small intestine is not equally responsive throughout its length. In animal experiments the ileum appears to be under greater sympathetic inhibitory control than the jejunum[28] and the same may be true in man. More selective studies of jejunocaecal and
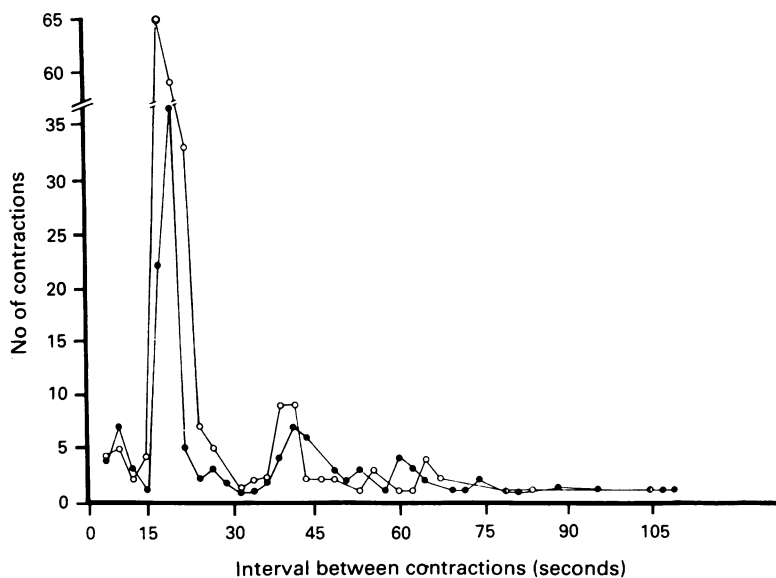

Figure 15: Frequency histogram of the interval between successive antral contractions comparing isoprenaline (closed circles) with control infusion (open circles). It can be seen that the mode occurs at 19 seconds with a second peak at 38 seconds.

ileocaecal transit will thus be required to further elucidate this problem.

It is also uncertain by which mechanism the adrenoreceptor modulation of small intestinal transit is achieved. The lack of observed effects of isoprenaline on the pattern of motor activity and the previously reported absence of effect of beta antagonists on antroduodenal motor pattern[11] do not indicate a major action on contractile rhythmicity. It must be accepted, however, that the technique of intraluminal manometry, as usually performed, is relatively crude and does not permit precise assessment of aboral propagation of small intestinal contractions and intraluminal content particularly after feeding. Further studies with closely spaced sensors, or techniques capable of directly measuring intraluminal force, such as those recently developed for the oesophagus,[29] will be required to answer such questions.

It is also possible that the beta adrenoreceptor mediated effects on transit were achieved through a direct effect on smooth muscle tone rather than motor pattern. This hypothesis is consistent with pharmacological localisation of beta-1 adrenoreceptor effects on smooth muscle particularly longitudinal muscle[30] rather than the myenteric plexus, and with the observed inhibition by isoprenaline of contraction amplitude, but not contraction pattern.

The observed transit effects might additionally have been mediated by modulation of another neuroactive agent, – for example, somatostatin,[31] or through an increase in intraluminal flow secondary to changes in epithelial,[17] or pancreatic secretion.[32]

In conclusion, our studies appear to have uncovered the presence of a tonically active beta adrenergically mediated pathway which operates to modulate nutrient transit in normal subjects and which varies in degree of expression between individuals. Explanations for this consistent variation in beta adrenergic tone include inter individual variation in sympathetic neuronal traffic, receptor numbers, receptor sensitivity, or end organ responsiveness. Further exploration of these possibilities is now indicated.

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