# Involvement of two different pathways in the motor effects of erythromycin on the gastric antrum in humans

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**Abstract**

*Background*—During the interdigestive state in humans, erythromycin 40 mg induces a premature activity front that starts in the stomach, while erythromycin 200 mg induces a prolonged period of enhanced antral contractile activity.

*Aims*—To study the involvement of a cholinergic pathway in the motor effects of erythromycin using the muscarinic antagonist atropine and the neural 5-HT$_1$ receptor agonist sumatriptan.

*Methods*—In 30 healthy volunteers, fasted antroduodenojejunal motor activity was studied by stationary manometry. Placebo (n=10), atropine (15 µg/kg intravenous bolus plus 15 µg/kg/h over 30 minutes; n=10), or sumatriptan (6 mg subcutaneously; n=10) was administered, followed by infusion of erythromycin 40 mg or 200 mg.

*Results*—After placebo, erythromycin 40 mg induced a premature activity front with gastric onset after 19.1 (1.7) minutes in all volunteers. After atropine, erythromycin 40 mg failed to induce a premature activity front during a 60 minute period in all volunteers (p<0.001), while sumatriptan prevented the induction of a premature activity front during a 60 minute period in all but one volunteer (p<0.005). The number of antral contractions and their mean amplitude in the 60 minutes after erythromycin 200 mg did not differ significantly after atropine or sumatriptan versus placebo.

*Conclusions*—The antral motor effects of erythromycin in humans are mediated via different pathways. The induction of a premature activity front is mediated through activation of an intrinsic cholinergic pathway, while the induction of enhanced antral contractile activity may be mediated via a pathway potentially involving activation of a muscular receptor.

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The macrolide antibiotic erythromycin enhances gastric emptying, both in gastroparetic patients and in healthy volunteers.[1][2] In the interdigestive state, dose dependent effects of erythromycin on the antroduodenojejunum were shown.[3] A low dose (40 mg) of erythromycin induces a premature activity front at the antral level which migrates caudally to the small intestine, while a higher dose (200 mg or 350 mg) induces a prolonged period of strong antral contractile activity which is not followed by a phase 1 and which does not migrate caudally.[3] At intermediate doses of erythromycin, a mixed motility pattern is not observed and with increasing doses of erythromycin an increasing proportion of subjects no longer display a premature antral activity front but prolonged strong antral contractile activity (personal observations). Whether or not this dose dependent effect of erythromycin in humans reflects the activation of two different pathways is not known.

There is considerable evidence that erythromycin exerts its gastrointestinal motor effects via direct activation of a motilin receptor.[4][5] In vitro studies in the rabbit showed that erythromycin increases antral contractile activity dose dependently via two mechanisms: at higher doses, an inotropic effect mediated through activation of smooth muscle motilin receptors and, at lower doses, a chronotropic effect mediated through activation of neural motilin receptors on cholinergic neurones.[6] Recently, binding studies further suggested the presence of two subtypes of motilin receptors, respectively located on nerve tissue and on smooth muscle in the rabbit.[7] In the dog, erythromycin increases antral contractile activity via a cholinergic mechanism.[8] In humans, it has been shown that the stimulatory effect of erythromycin on lower oesophageal sphincter pressure, and on gastric and gall bladder emptying is also mediated via activation of a cholinergic pathway.[9][10] In contrast, a non-cholinergic mechanism seems to underlie the contractile effect of erythromycin on the gastric fundus, although only a relatively low dose of atropine was used in this study.[11]

Recently, we showed that the 5-hydroxytryptamine (5-HT) receptor agonist sumatriptan behaves as an agonist at 5-HT$_{1P}$ receptors in the enteric nervous system in the guinea pig antrum.[12] Activation of presynaptic 5-HT$_{1P}$ receptors has been reported to inhibit the release of acetylcholine from cholinergic neurones.[13] Administration of sumatriptan has profound effects on both fasting and postprandial gastric motility in healthy subjects; sumatriptan delays gastric emptying of liquids and solids,[14] decreases fasting fundus tone,[15] and enhances postprandial receptive relaxation of the gastric fundus[16] as well as decreasing postprandial antral contractile activity.[16]
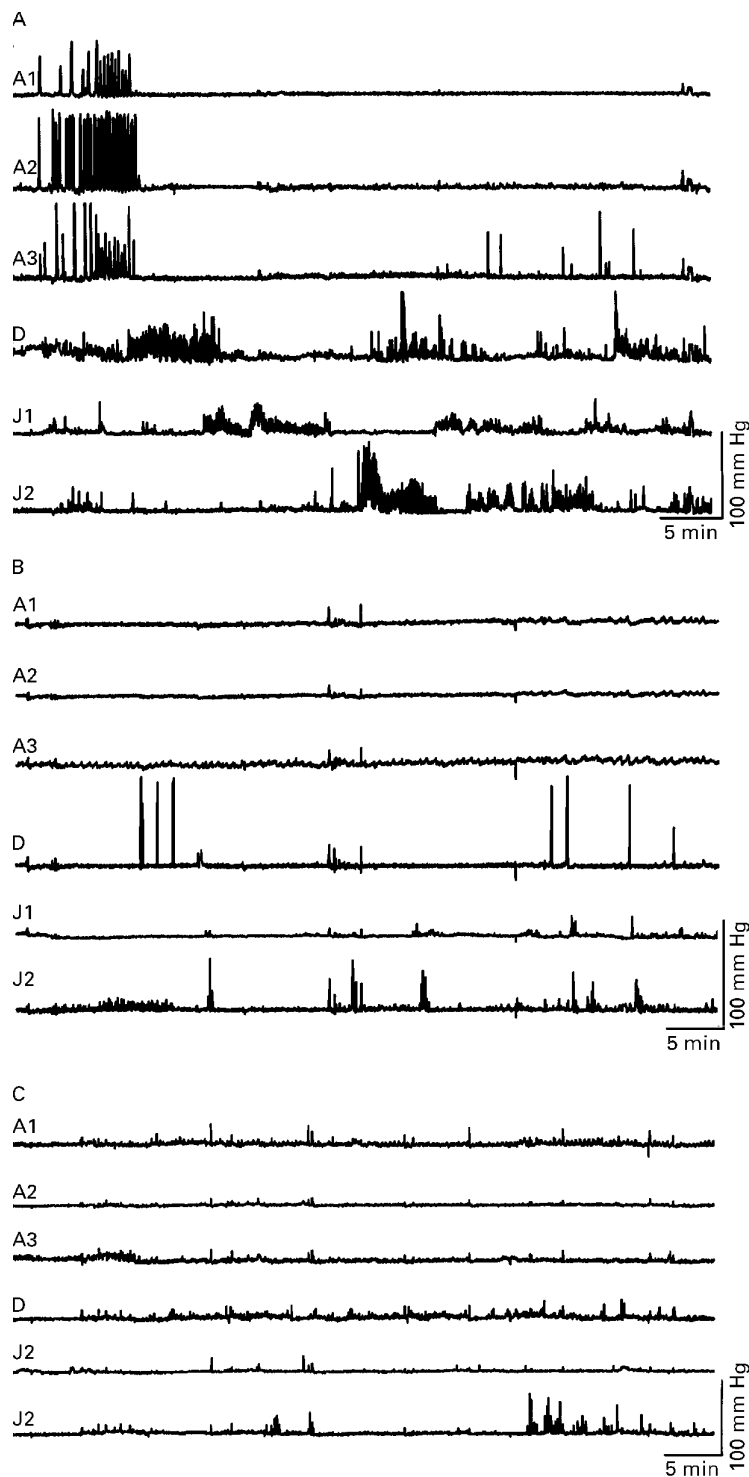
*Figure 1 Effect of atropine and sumatriptan on the initiation of an antral activity front by erythromycin 40 mg intravenously in a healthy volunteer. All traces begin at the start of the infusion of erythromycin, which lasted 10 minutes. (A) Erythromycin caused a premature activity front at the antral level that migrated caudally to the small intestine. (B) Prior administration of atropine blocked the generation of a premature activity front by erythromycin during a 60 minute period. (C) Prior administration of sumatriptan also blocked the generation of a premature activity front by erythromycin during a 60 minute period.*

and the 5-HT$_1$ receptor agonist sumatriptan to inhibit release of acetylcholine from cholinergic neurones.

## Materials and methods

### STUDY SUBJECTS

Thirty healthy volunteers were included in this study. None had a history of diabetes mellitus, gastrointestinal disease, or surgery, or was taking medication. Informed consent was obtained from each participant. The protocol had been previously approved by the Ethics Committee of the University Hospital of Leuven.

### RECORDING TECHNIQUE

Recordings of antroduodenojejunal intraluminal pressures were performed using an eight lumen polyvinyl catheter (outer diameter 6 mm) with a latex bag at its end that could be filled with mercury. The probe was introduced via the mouth and positioned under fluoroscopic control in such a way that the most distal of the three proximal sensors, which were 3 cm apart, was located in the antrum at the level of the pylorus or just distal to it. The three other sensors were located in the horizontal part of the duodenum and in the proximal jejunum, respectively at 17, 42, and 67 cm distally to the antropyloric recording sites. The two remaining catheters were used for filling and emptying of the mercury bag. This catheter assembly allowed us to keep at least one recording orifice in the distal antrum during the entire experiment and thus to monitor adequately the migrating motor complex simultaneously in the distal antrum, the duodenum, and the upper jejunum. The recording catheters were continuously perfused with water by means of a low compliance pneumo-hydraulic infusion pump (Arndorfer Medical Specialties Inc., Greendale, Wisconsin) at a flow rate of 0.4 ml/min, and were connected to external pressure transducers (Siemens Elema 746, Siemens, Iselin, New Jersey). Pressures were recorded on a polygraph (Siemens Elema Mingograph 82) using a paper speed of 5 mm/s.

### STUDY DESIGN

Following an overnight fast of at least 12 hours, the recording probe was introduced as described above and secured to the subject's chin with adhesive tape. An intravenous line was positioned into an antecubital vein on the right arm.

In all volunteers, gastrointestinal motility was recorded until the passage of one activity front of the migrating motor complex (MMC) at the antral and/or duodenal recording site. Ten minutes after the activity front passed at the most distal recording site, placebo or active drug was administered. In 10 subjects placebo (NaCl 0.9%, 1 ml intravenously) was given. Ten subjects received 6 mg sumatriptan (Imitrex, Glaxo-Wellcome, Brussels, Belgium) subcutaneously. This dose has been shown to be safe and effective in the control of migraine.[17] In the remaining 10 subjects atropine sulphate 15 µg/kg intravenous bolus followed by continuous infusion of 15 µg/kg/h

The purpose of the present study was to determine whether the dose dependent dual effects of erythromycin on antral motor activity in humans are mediated by different pathways and to identify the pathways possibly involved. We used atropine to block muscarinic receptors
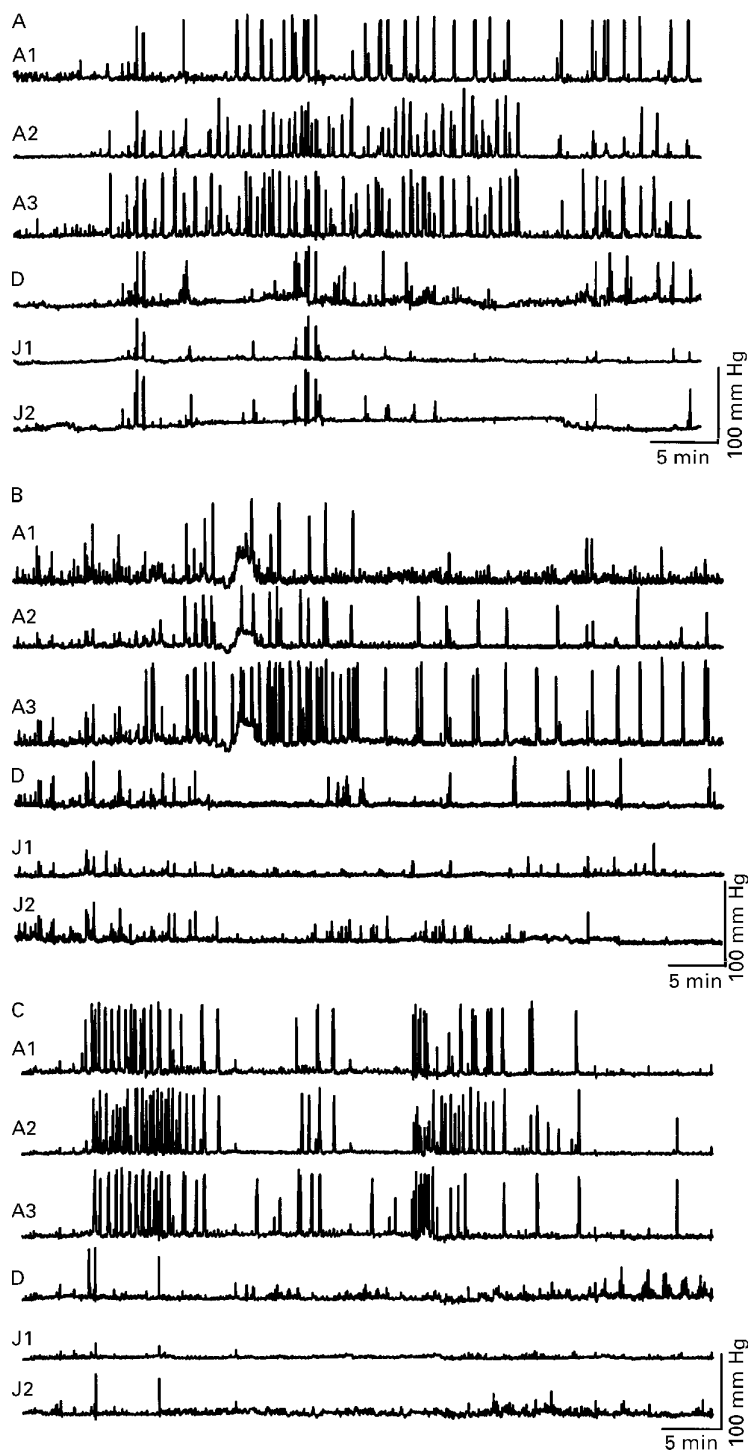
*Figure 2 Effect of atropine and sumatriptan on antral contractile activity induced by erythromycin 200 mg intravenously in a healthy volunteer. All traces begin at the start of the infusion of erythromycin, which lasted 10 minutes. (A) Erythromycin caused a burst of prolonged contractile activity at the antral level that did not migrate to the small intestine and was not followed by a phase 1. (B) Prior administration of atropine did not influence the occurrence of this prolonged antral contractile activity. (C) Prior administration of sumatriptan also did not block the erythromycin induced prolonged antral contractile activity.*

over 30 minutes was administered, while arterial pulse frequency was continuously monitored. Ten minutes later, half the subjects in each study group received erythromycin lactobionate (Abbott, Ottignies, Belgium) 40 mg, while the other half received erythromycin lactobionate 200 mg. Both doses of erythromycin

lactobionate were dissolved in 100 ml of NaCl 0.9 % and given in a 10 minute intravenous infusion. Motility was recorded until another activity front of the MMC after the administration of erythromycin had occurred at the antral and/or duodenal recording site.

DATA ANALYSIS
Analysis of the recordings of gastroduodenojejunal motor activity was performed by two of the authors (JT and BC) independently; both were blinded to the drug regimen. Visual inspection allowed continuous identification of the most distal antral recording site as the catheter that recorded up to three pressure waves per minute (antral waves) just proximal to the catheter that recorded up to 12 contractions per minute (duodenal waves) or to the catheter that exhibited a mixture of antral and duodenal waves. The different phases of the MMC were identified according to well established criteria.[3][18] The cut off value for calculation of contractions was $\geq 10$ mm Hg. In the group that received erythromycin 40 mg, the number of activity fronts occurring at the antral level during a 60 minute period starting from administration of erythromycin was calculated and compared after placebo versus atropine and sumatriptan using Fisher's exact test. In the group that received erythromycin 200 mg, the total number and the mean amplitude of antral contractions recorded in the most distal antral channel in the 60 minutes starting from administration of erythromycin was calculated and compared using the unpaired Student's *t* test. Statistical analyses were performed using SAS/STAT software (SAS Institute Inc., Cary, North Carolina). Differences were considered to be significant at the 5% level. Results are given as mean (SEM).

**Results**
In the placebo group, administration of erythromycin 40 mg induced a typical premature activity front in all five volunteers tested after 19.1 (1.7) minutes (range 15–25 minutes) (fig 1A). This activity front always started in the antrum and migrated caudally to the jejunum. It was followed by a phase 1 which lasted for 26 (8.4) minutes. Characteristics of the erythromycin induced activity front did not differ from spontaneously occurring activity fronts (data not shown).

In all volunteers receiving atropine, arterial pulse frequency increased from 60 (2.3) to 89.3 (10.6) beats/min (p<0.01). Administration of sumatriptan induced a premature activity front at the jejunal level in 6 of 10 subjects after 4.5 (0.4) minutes, as previously described.[19]

Prior administration of atropine prevented the occurrence of any premature antral activity front after erythromycin 40 mg in all volunteers tested (p<0.001) (fig 1B). In all volunteers, infusion of erythromycin 40 mg after atropine was followed by persisting phase 1 activity at the antral level which lasted for 31 (18.6) minutes, after which phase 2 activity was observed.

After sumatriptan 6 mg subcutaneously, administration of erythromycin 40 mg intravenously failed to induce a premature activity front at the antral level within a 60 minute period after starting the infusion in four of five volunteers ($p<0.005$) (fig 1C). Instead, phase 1 activity persisted for 36 (7.7) minutes and was followed by phase 2 activity. Only in one volunteer did administration of erythromycin 40 mg after sumatriptan induce an antral activity front which started after 21 minutes.

In the placebo group, administration of erythromycin 200 mg intravenously induced bursts of strong rhythmic contractions in the antrum. These antral contractions were not propagated to the small intestine and were not followed by a phase 1, but instead by a prolonged period of increased antral contractile activity (fig 2A). The total number of antral contractions recorded at the most distal antral channel and calculated during a 60 minute period after administration of erythromycin 200 mg intravenously in the placebo group was 52 (7). The mean amplitude of the total number of antral contractions in the placebo group was 75.5 (9.1) mm Hg.

After pretreatment with atropine, administration of erythromycin 200 mg was still able to induce strong antral contractions which were not propagated and not followed by a phase 1. The total number of antral contractions after atropine and erythromycin 200 mg did not differ significantly compared with placebo (55 (14) versus 52 (7)) (fig 2B). The mean amplitude of antral contractions also did not differ significantly compared with placebo (76 (9.9) versus 75.5 (9.1)).

After sumatriptan, administration of erythromycin 200 mg still induced a burst of antral contractions that did not migrate caudally to the small intestine and which was not followed by phase 1 activity. Prior administration of sumatriptan did not influence the total number of antral contractions (58 (12) versus 52 (7)) (fig 2C) or the mean amplitude (60.4 (5.5) versus 75.5 (9.1)).

After subcutaneous administration of sumatriptan, some subjects reported feelings of heaviness in the neck or head or lightheadedness, symptoms that have been reported to occur after sumatriptan.[17] Intravenous administration of atropine caused a feeling of increased heart rate (palpitations) in some subjects and one volunteer reported moderate blurred vision.

## Discussion

The current study confirms our earlier findings that erythromycin administered intravenously in healthy volunteers has a dose related effect on the interdigestive motility of the stomach and the small intestine.[3] A low dose (40 mg) of erythromycin induced a premature activity front at the antral level which migrated through the small intestine. A higher dose of erythromycin (200 mg) induced strong and prolonged antral contractile activity which was not propagated to the small intestine. The effect of a single dose of atropine or sumatriptan was used to investigate the effect of both treatments on the antral motor effects of two different doses of erythromycin. Prior administration of the muscarinic antagonist atropine blocked the generation of a premature activity front in the stomach by a low dose of erythromycin. However, prolonged antral contractile activity induced by a high dose of erythromycin remained unaffected by atropine. Similar findings were observed after administration of the 5-HT$_1$ receptor agonist sumatriptan. Erythromycin induced activity fronts at the antral level were completely abolished while strong antral contractions after a high dose of erythromycin were still present after administration of sumatriptan.

The precise mechanism through which erythromycin alters gastric motility is incompletely understood. Numerous in vitro data strongly suggest that erythromycin behaves as an agonist on motilin receptors.[4 5] In view of the putative role of motilin in the control of interdigestive motility,[20] the initiation of a premature gastric activity front by a low dose of erythromycin is compatible with a motilin agonistic effect of the drug. Furthermore, in humans, the premature activity front is not accompanied by an endogenous plasma motilin peak, excluding an erythromycin induced release of motilin.[3] The mechanism by which higher doses of erythromycin stimulate antral contractile activity is still unclear but, again, does not involve the release of motilin.[3]

Our results seem to indicate that in humans two different pathways are involved in the dose related effect of erythromycin on interdigestive antral motility. However, by using just one dose of atropine, a cholinergic mechanism underlying the effect of 200 mg erythromycin on antral motor activity cannot be entirely discarded. Nonetheless, the dose of atropine used in our study is the maximal dose safely achievable in healthy subjects. It has been shown in dogs that a high dose of atropine (100 µg/kg) did block both the occurrence of MMCs induced by a low dose of erythromycin and the induction of strong antral contractions after a high dose of erythromycin.[8] The induction of a premature gastric activity front requires activation of a cholinergic pathway as it is blocked by the muscarinic antagonist atropine. In in vitro studies in the guinea pig, we showed that the 5-HT$_1$ receptor agonist sumatriptan behaves as an agonist at 5-HT$_{1P}$ receptors in the enteric nervous system.[12] Activation of presynaptic 5-HT$_{1P}$ receptors has been reported to inhibit the release of acetylcholine from cholinergic neurones.[13] Therefore, our observation that pretreatment with sumatriptan inhibits the induction of a premature activity front by erythromycin is also compatible with the requirement of an enteric neural cholinergic pathway. Recent preliminary observations suggest that the effect of motilin on antral motor activity in humans is also mediated through the activation of cholinergic neurones.[21] Therefore, we hypothesise that low doses of erythromycin induce a premature activity front by acting on motilin receptors on cholinergic neurones in the antrum.

Alternatively, as both sumatriptan and atropine relax gastric fundus tone, functional antagonism by a relaxation of the fundus causing inhibition of a premature activity front induced by a low dose of erythromycin could explain the observed effects. However, there are no in vivo or in vitro data available that would support the presence of such a pathway.

Both atropine and sumatriptan failed to inhibit the induction of prolonged rhythmic antral contractile activity by a high dose of erythromycin, indicating that this effect is not mediated through a cholinergic mechanism. It may reflect activation of a non-cholinergic neural pathway, or activation of a pathway probably involving a muscular (motilin) receptor by erythromycin.

The available data on the localisation of motilin receptors show some variation among different species. In the dog, in vitro and in vivo studies have showed that motilin receptors are neurally located, mainly on cholinergic nerve fibres.[8 22–24] Initially, in vitro studies using human and rabbit gut tissue, suggested that motilin receptors are exclusively located on smooth muscle cells in these species.[25–28] Nonetheless, recent in vitro studies clearly showed that a neural motilin receptor is also present in the rabbit antrum.[6 7 29] The dose dependency and the difference in pathway of activation we observed in humans are in perfect agreement with data obtained in vitro in the rabbit antrum.[6] On rabbit antral circular muscle strips, erythromycin displays a dual, dose related contractile effect. At a micromolar dose, erythromycin causes a contraction of antral circular muscle, which is tetrodotoxin, atropine, and hexamethonium resistant, indicating that the contractile effect appears to be mediated directly on the smooth muscle. At a lower dose of erythromycin, the frequency of antral phasic contractions induced by exogenous bethanechol or substance P is increased, an effect that is tetrodotoxin and atropine sensitive.[6] These data implicate that in the rabbit antrum, two subtypes of motilin receptors are present: a "high affinity" receptor located on nerve fibres, probably cholinergic in nature, and a "low affinity" receptor located on smooth muscle cells. These subtypes have been further substantiated using radioligand binding studies.[7] It was convincingly shown that in the rabbit antrum two motilin receptor subtypes, located respectively neurally and on smooth muscle cells, are present, with the neural receptor displaying a higher affinity for native motilin and erythromycin than the myogenic receptor, suggesting that these two receptors have different structural characteristics.[7]

Our findings are also compatible with the presence of two motilin receptor types in humans: a low dose of erythromycin may generate a premature activity front via activation of a high affinity motilin receptor on cholinergic neurones; higher doses of erythromycin may activate a lower affinity receptor resulting in bursts of strong antral contractions. In view of previous in vitro studies in humans,[27–29] and in analogy to the observation in animals,[6 7] we hypothesise the latter receptor to be a smooth muscle motilin receptor. However, to confirm this hypothesis, supplementary studies investigating the effect of different doses of the endogenous agonist, motilin itself and a selective motilin receptor antagonist on human antral motor activity are warranted.

It is unclear why, during administration of higher doses of erythromycin, migration of an erythromycin induced activity front is no longer observed. However, it is possible that the motility pattern that is induced by activation of a pathway, probably involving activation of a muscular motilin receptor by a high dose of erythromycin, inhibits the neurally mediated generation of an activity front.

In conclusion, the present study confirms earlier studies that erythromycin stimulates interdigestive antral motor activity in different ways and in a dose dependent manner. We showed for the first time in humans that the dose dependency of the erythromycin induced effects is probably due to activation of two different pathways. A low dose of erythromycin induces an antral activity front via activation of a cholinergic pathway, while a higher dose produces prolonged antral contractile activity which does not require activation of a cholinergic pathway. We hypothesise that the latter reflects activation of a pathway probably involving a muscular motilin receptor. Which one of these receptor subtypes is involved in the prokinetic properties of erythromycin in vivo in humans awaits further studies.

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