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# Motilin receptor in GtoPdb v.2021.2

Anthony P. Davenport[1], Takio Kitazawa[2] and Gareth Sanger[3]

1. University of Cambridge, UK
2. Rakuno Gakuen University, Japan
3. Queen Mary University of London, UK

## Abstract

Motilin receptors (**provisional nomenclature**) are activated by motilin, a 22 amino-acid peptide derived from a precursor (*MLN*, P12872), which may also generate a motilin-associated peptide. There are significant species differences in the structure of motilin and its receptor. In humans and large mammals such as dog, activation of these receptors by motilin released from endocrine cells in the duodenal mucosa during fasting, induces propulsive phase III movements. This activity is associated with promoting hunger in humans. Drugs and other non-peptide compounds which activate the motilin receptor may generate a more long-lasting ability to increase cholinergic activity within the upper gut, to promote gastrointestinal motility; this activity is suggested to be responsible for the gastrointestinal prokinetic effects of certain macrolide antibiotics (often called motilides; *e.g.* erythromycin, azithromycin), although for many of these molecules the evidence is sparse. Relatively high doses may induce vomiting and in humans, nausea.

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## References

1. Asakawa A, Inui A, Momose K, Ueno N, Fujino MA and Kasuga M. (1998) Motilin increases food intake in mice. *Peptides* **19**: 987-90 [PMID:9700745]
2. Barshop K and Kuo B. (2015) The investigational drug camicinal for the treatment of gastroparesis. *Expert Opin Investig Drugs* **24**: 133-140 [PMID:25341626]

3. Boivin MA, Carey MC and Levy H. (2003) Erythromycin accelerates gastric emptying in a dose-response manner in healthy subjects. *Pharmacotherapy* **23**: 5-8 [PMID:12523456]
4. Broad J and Sanger GJ. (2013) The antibiotic azithromycin is a motilin receptor agonist in human stomach: comparison with erythromycin. *Br J Pharmacol* **168**: 1859-67 [PMID:23190027]
5. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
6. Carreras CW, Siani MA, Santi DV and Dillon SB. (2002) Stable expression of a synthetic gene for the human motilin receptor: use in an aequorin-based receptor activation assay. *Anal Biochem* **300**: 146-51 [PMID:11779105]
7. Clark MJ, Wright T, Bertrand PP, Bornstein JC, Jenkinson KM, Verlinden M and Furness JB. (1999) Erythromycin derivatives ABT 229 and GM 611 act on motilin receptors in the rabbit duodenum. *Clin Exp Pharmacol Physiol* **26**: 242-5 [PMID:10081621]
8. Coulie B, Matsuura B, Dong M, Hadac EM, Pinon DI, Feighner SD, Howard AD and Miller LJ. (2001) Identification of peptide ligand-binding domains within the human motilin receptor using photoaffinity labeling. *J Biol Chem* **276**: 35518-22 [PMID:11461914]
9. Dass NB, Hill J, Muir A, Testa T, Wise A and Sanger GJ. (2003) The rabbit motilin receptor: molecular characterisation and pharmacology. *Br J Pharmacol* **140**: 948-54 [PMID:14504130]
10. Depoortere I and Peeters TL. (1995) Transduction mechanism of motilin and motilides in rabbit duodenal smooth muscle. *Regul Pept* **55**: 227-35 [PMID:7761622]
11. Farrugia G, Macielag MJ, Peeters TL, Sarr MG, Galdes A and Szurszewski JH. (1997) Motilin and OHM-11526 activate a calcium current in human and canine jejunal circular smooth muscle. *Am J Physiol* **273**: G404-12 [PMID:9277420]
12. Feighner SD, Tan CP, McKee KK, Palyha OC, Hreniuk DL, Pong SS, Austin CP, Figueroa D, MacNeil D and Cascieri MA *et al.*. (1999) Receptor for motilin identified in the human gastrointestinal system. *Science* **284**: 2184-8 [PMID:10381885]
13. Feng X, Peeters TL and Tang M. (2007) Motilin activates neurons in the rat amygdala and increases gastric motility. *Peptides* **28**: 625-31 [PMID:17222944]
14. Guan Y, Tang M, Jiang Z and Peeters TL. (2003) Excitatory effects of motilin in the hippocampus on gastric motility in rats. *Brain Res* **984**: 33-41 [PMID:12932837]
15. Haramura M, Okamachi A, Tsuzuki K, Yogo K, Ikuta M, Kozono T, Takanashi H and Murayama E. (2002) Design and synthesis of motilin antagonists derived from the [1-4] fragment of porcine motilin. *J Med Chem* **45**: 670-5 [PMID:11806718]
16. He J, Irwin DM, Chen R and Zhang YP. (2010) Stepwise loss of motilin and its specific receptor genes in rodents. *J Mol Endocrinol* **44**: 37-44 [PMID:19696113]
17. Holst B, Cygankiewicz A, Jensen TH, Ankersen M and Schwartz TW. (2003) High constitutive signaling of the ghrelin receptor--identification of a potent inverse agonist. *Mol Endocrinol* **17**: 2201-10 [PMID:12907757]
18. Jadcherla SR and Berseth CL. (2002) Effect of erythromycin on gastroduodenal contractile activity in developing neonates. *J Pediatr Gastroenterol Nutr* **34**: 16-22 [PMID:11753158]
19. Jadcherla SR, Klee G and Berseth CL. (1997) Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. *Pediatr Res* **42**: 365-9 [PMID:9284278]
20. Jia YD, Liu CQ, Tang M and Jiang ZY. (2007) Expression of motilin in the hypothalamus and the effect of central erythromycin on gastric motility in diabetic rats. *Neurosci Bull* **23**: 75-82 [PMID:17592529]
21. Kamerling IM, van Haarst AD, Burggraaf J, Schoemaker RC, de Kam ML, Heinzerling H, Cohen AF and Masclee AA. (2004) Effects of a nonpeptide motilin receptor antagonist on proximal gastric motor function. *Br J Clin Pharmacol* **57**: 393-401 [PMID:15025736]
22. Kitazawa T, Taneike T and Ohga A. (1997) Functional characterization of neural and smooth muscle motilin receptors in the chicken proventriculus and ileum. *Regul Pept* **71**: 87-95 [PMID:9416990]
23. Koga H, Sato T, Tsuzuki K, Onoda H, Kuboniwa H and Takanashi H. (1994) Potent, acid-stable and orally active macrolide-type motilin receptor agonists, GM-611 and the derivatives. *Bioorg Med Chem Lett* **4**: 1347-1352
24. Li JJ, Chao HG, Wang H, Tino JA, Lawrence RM, Ewing WR, Ma Z, Yan M, Slusarchyk D and Seethala R *et al.*. (2004) Discovery of a potent and novel motilin agonist. *J Med Chem* **47**: 1704-8 [PMID:15027861]
25. Luiking YC, Peeters TL, Stolk MF, Nieuwenhuijs VB, Portincasa P, Depoortere I, van Berge Henegouwen GP and Akkermans LM. (1998) Motilin induces gall bladder emptying and antral contractions in the fasted state in humans. *Gut* **42**: 830-5 [PMID:9691922]
26. Maguire JJ, Kuc RE and Davenport AP. (2004) Motilin mediates vasoconstriction in human coronary artery *in vitro*. *Proceedings of the British Pharmacological Society, $pA_2$ online*: -
27. Matsuura B, Dong M, Coulie B, Pinon DI and Miller LJ. (2005) Demonstration of a specific site of covalent labeling of the human motilin receptor using a biologically active photolabile motilin analog. *J Pharmacol Exp Ther* **313**: 1101-8 [PMID:15677347]

28. Matsuura B, Dong M and Miller LJ. (2002) Differential determinants for peptide and non-peptidyl ligand binding to the motilin receptor. Critical role of second extracellular loop for peptide binding and action. *J Biol Chem* **277**: 9834-9 [PMID:11781320]
29. Matsuura B, Dong M, Naik S, Miller LJ and Onji M. (2006) Differential contributions of motilin receptor extracellular domains for peptide and non-peptidyl agonist binding and activity. *J Biol Chem* **281**: 12390-6 [PMID:16531413]
30. McKee KK, Tan CP, Palyha OC, Liu J, Feighner SD, Hreniuk DL, Smith RG, Howard AD and Van der Ploeg LH. (1997) Cloning and characterization of two human G protein-coupled receptor genes (GPR38 and GPR39) related to the growth hormone secretagogue and neurotensin receptors. *Genomics* **46**: 426-34 [PMID:9441746]
31. Miller P, Roy A, St-Pierre S, Dagenais M, Lapointe R and Poitras P. (2000) Motilin receptors in the human antrum. *Am J Physiol Gastrointest Liver Physiol* **278**: G18-23 [PMID:10644557]
32. Mitselos A, Depoortere I and Peeters TL. (2007) Delineation of the motilin domain involved in desensitization and internalization of the motilin receptor by using full and partial antagonists. *Biochem Pharmacol* **73**: 115-24 [PMID:17074305]
33. Momose K, Inui A, Asakawa A, Ueno N, Nakajima M and Kasuga M. (1998) Anxiolytic effect of motilin and reversal with GM-109, a motilin antagonist, in mice. *Peptides* **19**: 1739-42 [PMID:9880080]
34. Nieuwenhuijs VB, van Duijvenbode-Beumer H, Verheem A, Visser MR, Verhoef J, Gooszen HG and Akkermans LM. (1999) The effects of ABT-229 and octreotide on interdigestive small bowel motility, bacterial overgrowth and bacterial translocation in rats. *Eur J Clin Invest* **29**: 33-40 [PMID:10092986]
35. Rodríguez-Sinovas A, Jiménez M, De Clercq P, Peeters TL and Vergara P. (1997) Rhythmic oscillating complexes in gastrointestinal tract of chickens: a role for motilin. *Am J Physiol* **272**: G916-22 [PMID:9142926]
36. Sanger GJ. (2014) Ghrelin and motilin receptor agonists: time to introduce bias into drug design. *Neurogastroenterol Motil* **26**: 149-55 [PMID:24438586]
37. Sanger GJ, Holbrook JD and Andrews PL. (2011) The translational value of rodent gastrointestinal functions: a cautionary tale. *Trends Pharmacol Sci* **32**: 402-9 [PMID:21531468]
38. Sanger GJ, Wang Y, Hobson A and Broad J. (2013) Motilin: towards a new understanding of the gastrointestinal neuropharmacology and therapeutic use of motilin receptor agonists. *Br J Pharmacol* **170**: 1323-32 [PMID:23189978]
39. Sanger GJ, Westaway SM, Barnes AA, Macpherson DT, Muir AI, Jarvie EM, Bolton VN, Cellek S, Näslund E and Hellström PM *et al.*. (2009) GSK962040: a small molecule, selective motilin receptor agonist, effective as a stimulant of human and rabbit gastrointestinal motility. *Neurogastroenterol Motil* **21**: 657-64, e30-1 [PMID:19374732]
40. Sengupta S, Modak P, McCauley N and O'Donnell LJ. (2006) Effect of oral clarithromycin on gall-bladder motility in normal subjects and those with gall-stones. *Aliment Pharmacol Ther* **24**: 95-9 [PMID:16803607]
41. Sharma SS, Bhargava N and Mathur SC. (1995) Effect of oral erythromycin on colonic transit in patients with idiopathic constipation. A pilot study. *Dig Dis Sci* **40**: 2446-9 [PMID:7587829]
42. Strunz U, Domschke W, Mitznegg P, Domschke S, Schubert E, Wünsch E, Jaeger E and Demling L. (1975) Analysis of the motor effects of 13-norleucine motilin on the rabbit, guinea pig, rat, and human alimentary tract in vitro. *Gastroenterology* **68**: 1485-91 [PMID:1132629]
43. Sudo H, Yoshida S, Ozaki K, Muramatsu H, Onoma M, Yogo K, Kamei K, Cynshi O, Kuromaru O and Peeters TL *et al.*. (2008) Oral administration of MA-2029, a novel selective and competitive motilin receptor antagonist, inhibits motilin-induced intestinal contractions and visceral pain in rabbits. *Eur J Pharmacol* **581**: 296-305 [PMID:18164286]
44. Takanashi H, Yogo K, Ozaki K, Ikuta M, Akima M, Koga H and Nabata H. (1995) GM-109: a novel, selective motilin receptor antagonist in the smooth muscle of the rabbit small intestine. *J Pharmacol Exp Ther* **273**: 624-8 [PMID:7752063]
45. Takanashi H, Yogo K, Ozaki K, Koga H, Itoh Z and Omura S. (2007) In vitro pharmacological characterization of mitemcinal (GM-611), the first acid-resistant non-peptide motilin receptor agonist, in smooth muscle of rabbit small intestine. *Pharmacology* **79**: 137-48 [PMID:17183187]
46. Takeshita E, Matsuura B, Dong M, Miller LJ, Matsui H and Onji M. (2006) Molecular characterization and distribution of motilin family receptors in the human gastrointestinal tract. *J Gastroenterol* **41**: 223-30 [PMID:16699856]
47. Thielemans L, Depoortere I, Perret J, Robberecht P, Liu Y, Thijs T, Carreras C, Burgeon E and Peeters TL. (2005) Desensitization of the human motilin receptor by motilides. *J Pharmacol Exp Ther* **313**: 1397-405 [PMID:15764739]
48. Thielemans L, Depoortere I, Van Assche G, Bender E and Peeters TL. (2001) Demonstration of a functional motilin receptor in TE671 cells from human cerebellum. *Brain Res* **895**: 119-28 [PMID:11259768]
49. Thielemans L, Depoortere I, Vanden Broeck J and Peeters TL. (2002) The motilin pharmacophore in CHO cells expressing the human motilin receptor. *Biochem Biophys Res*

*Commun* **293**: 1223-7 [PMID:12054506]
50. Van Assche G, Depoortere I, Thijs T, Missiaen L, Penninckx F, Takanashi H, Geboes K, Janssens J and Peeters TL. (2001) Contractile effects and intracellular Ca2+ signalling induced by motilin and erythromycin in the circular smooth muscle of human colon. *Neurogastroenterol Motil* **13**: 27-35 [PMID:11169123]
51. Westaway SM and Sanger GJ. (2009) The identification of and rationale for drugs which act at the motilin receptor. *Prog Med Chem* **48**: 31-80 [PMID:21544957]
52. Yamamoto I, Kaiya H, Tsutsui C, Sakai T, Tsukada A, Miyazato M and Tanaka M. (2008) Primary structure, tissue distribution, and biological activity of chicken motilin receptor. *Gen Comp Endocrinol* **156**: 509-14 [PMID:18433751]
53. Zhang S, Teraoka H, Kaiya H and Kitazawa T. (2021) Motilin- and ghrelin-induced contractions in isolated gastrointestinal strips from three species of frogs. *Gen Comp Endocrinol* **300**: 113649 [PMID:33153968]
54. Zhao DM, Xue HH, Chida K, Suda T, Oki Y, Kanai M, Uchida C, Ichiyama A and Nakamura H. (2000) Effect of erythromycin on ATP-induced intracellular calcium response in A549 cells. *Am J Physiol Lung Cell Mol Physiol* **278**: L726-36 [PMID:10749750]