Motilin receptor

Overview: Motilin receptors (**provisional nomenclature**) are activated by motilin (*MLN*, P12872), a 22 amino-acid peptide derived from a precursor (*MLN*, P12872), which may also generate a motilin-associated peptide (*MLN*, P12872). Activation of these receptors by endogenous motilin released from endocrine cells within the mucosa of the duodenum during fasting, induces propulsive phase III movements, part of the gastric migrating motor complex, and promotes the sensation of hunger. 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), although for many of these molecules the evidence is sparse. Relatively high doses of these compounds may induce vomiting and in humans, nausea.

Family structure

Nomenclature	motilin receptor
HGNC, UniProt	*MLNR*, O43193
Endogenous agonists	motilin (*MLN*, P12872) [3, 11, 12, 13]
Agonists	alemcinal [23], erythromycin [5, 23], azithromycin [2]
Selective agonists	camicinal [1, 20], mitemcinal [9, 22] – Rabbit
Selective antagonists	MA-2029 (pA_2 9.2) [21], GM-109 (pIC$_{50}$ 8) [6] – Rabbit
Labelled ligands	[^{125}I]motilin (human) (Agonist) [5]

Comments: In terms of structure, the motilin receptor has closest homology with the ghrelin receptor. Thus, the human motilin receptor shares 52% overall amino acid identity with the ghrelin receptor and 86% in the transmembrane regions [7, 22, 23]. However, differences between the N-terminus regions of these receptors means that their cognate peptide ligands do not readily activate each other [4, 20]. In laboratory rodents, the gene encoding the motilin percursor appears to be absent, while the receptor appears to be a pseudogene [7, 18]. Functions of motilin (*MLN*, P12872) are not usually detected in rodents, although brain and other responses to motilin and the macrolide alemcinal have been reported and the mechanism of these actions is obscure [14, 16]. Notably, in some non-laboratory rodents (*e.g.* the North American kangaroo rat (*Dipodomys*) and mouse (*Microdipodops*) a functional form of motilin may exist but the motilin receptor is non-functional [10]. Marked differences in ligand affinities for the motilin receptor in dogs and humans may be explained by significant differences in receptor structure [19]. Note that for the complex macrolide structures, selectivity of action has often not been rigorously examined and other actions are possible (*e.g.* P2X inhibition by erythromycin; [25]). Small molecule motilin receptor agonists are now described [10, 20, 24]. The motilin receptor does not appear to have constitutive activity [8]. Although not proven, the existence of biased agonism at the receptor has been suggested [13, 15, 17]. A truncated 5-transmembrane structure has been identified but this is without activity when transfected into a host cell [5]. Receptor dimerisation has not been reported.

Further reading on Motilin receptor

Deloose E *et al.* (2019) Motilin: from gastric motility stimulation to hunger signalling. *Nat Rev Endocrinol* **15**: 238-250 [PMID:30675023]

Sanger GJ *et al.* (2016) Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* **13**: 38-48 [PMID:26392067]

Singaram K *et al.* (2020) Motilin: a panoply of communications between the gut, brain, and pancreas. *Expert Rev Gastroenterol Hepatol* **14**: 103-111 [PMID:31996050]

References

1. Barshop K *et al.* (2015) [25341626]
2. Broad J *et al.* (2013) [23190027]
3. Coulie B *et al.* (2001) [11461914]
4. Dass NB *et al.* (2003) [14504130]
5. Feighner SD *et al.* (1999) [10381885]
6. Haramura M *et al.* (2002) [11806718]
7. He J *et al.* (2010) [19696113]
8. Holst B *et al.* (2003) [12907757]
9. Koga H *et al.* (1994) Potent, acid-stable and orally active macrolide-type motilin receptor agonists, GM-611 and the derivatives. *Bioorg. Med. Chem. Lett.* **4**: 1347-1352
10. Li JJ *et al.* (2004) [15027861]
11. Matsuura B *et al.* (2005) [15677347]
12. Matsuura B *et al.* (2002) [11781320]
13. Matsuura B *et al.* (2006) [16531413]
14. McKee KK *et al.* (1997) [9441746]
15. Mitselos A *et al.* (2007) [17074305]
16. Nieuwenhuijs VB *et al.* (1999) [10092986]
17. Sanger GJ. (2014) [24438586]
18. Sanger GJ *et al.* (2011) [21531468]
19. Sanger GJ *et al.* (2013) [23189978]
20. Sanger GJ *et al.* (2009) [19374732]
21. Sudo H *et al.* (2008) [18164286]
22. Takanashi H *et al.* (2007) [17183187]
23. Thielemans L *et al.* (2005) [15764739]
24. Westaway SM *et al.* (2009) [21544957]