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MINI-REVIEW ARTICLE

A Review on Motilin: Functioning Cellular and Molecular Mechanism, Pathology and Clinical Significance

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Abstract: The discovery of the motilin receptor and advances in techniques warrant a reevaluation of motilin's digestive role. Despite similarities with ghrelin in genomic structure and gastrointestinal effects, motilin and ghrelin receptors are specific and do not cross-react. In rodents, motilin's function is limited due to receptor pseudogenes. While motilin stimulates enteric cholinergic activity rather than directly contracting muscle, its effects differ from the more prolonged impact of agonists like erythromycin and GSK962040. Furthermore, while motilin's receptor is highly expressed in muscle tissue, motilin primarily acts by promoting enteric cholinergic activity rather than directly inducing muscle contraction. The use of erythromycin, an antibiotic, as a motilin receptor agonist to accelerate gastric emptying in patients has raised safety concerns, particularly regarding the potential for increased antibiotic resistance. Motilide substitutes have not been successful, but new non-motilide small-molecule agonists are in trials for conditions like diabetic gastroparesis. This underscores the importance of balancing artificial models, structural data, and animal studies in pharmacology. In conclusion, the study of motilin and its receptor provides an important example for translational pharmacologists, emphasizing the need to avoid overreliance on artificial systems, structural data, and animal models when developing new therapeutic approaches. The complexities of motilin's actions and the challenges associated with receptor agonism highlight the importance of continued research and innovation in the field of gastrointestinal pharmacology.

Keywords: Motilin, gastrointestinal, motilin receptor, hormone motilin, cholinergic activity, diabetic gastroparesis.

1. INTRODUCTION

Peptides that are released into the portal system to target particular cells are known as gastrointestinal hormones. Since they control the smooth muscle contractions of the gastrointestinal system and enable food to travel along the gastrointestinal tract, gastrointestinal hormones are a crucial component of the digestive system [1]. The entero-endocrine cells (Mo cells) in the upper small intestine release the hormone motilin on a cyclical basis while the body is fasting. Undigested food in the stomach and small intestine moves into the large intestine as a result of motilin's stimulation of these organs' motility. The inter-digestive myoelectric complex or the Migrating Motor Complex (MMC) are other names for this movement. Additionally, motilin increases the release of somatostatin, pancreatic polypeptide, and pepsin from the main cells of the stomach. Disturbed gastrointestinal motility has been linked to motilin [2]. During pregnancy, when the gastrointestinal system is hypomotile, motilin levels are decreased. Additionally, the diet consumed affects the motilin level. With the consumption of glucose and fat, motilin levels decrease [3].

Data was obtained from database searches (Scopus, Embase, EBSCO, PubMed, and Google Scholar) using keywords neurological disorders, pathophysiology, management strategies, pharmacotherapy, and non-pharmacological interventions.

2. FUNCTIONS OF MOTILIN

Multiple organs are affected by motilin. It promotes GI tract motility, increased pancreatic insulin release, increased gall bladder emptying, and increased hunger [2]. By controlling the migratory motor complex known as hunger contraction, motilin affects the movement of the digestive tract [4]. During the fasting and inter-digestive periods, the migratory motor complex takes place. At intervals of 1.5 to 2 hours, the migrating motor complex travels from the stomach to the terminal ileum. Undigested food is transported by the migrating motor complexes, which also help bacteria move from the small to the large intestine and prevent bacteria from moving from the large to the terminal ileum. There are three steps to the migrating motor complexes. The digestive tract's smooth muscle is dormant during phase I. The peristaltic activity of

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the digestive tract increases during Phase II. Phase III of the migrating motor complex is the phase with the highest contractile activity. The pylorus of the stomach is still open throughout phase III, allowing undigested food to pass into the small intestine [2]. By altering the brain's neurocircuit, motilin has recently come to be thought of as a key orexigenic hormone [4].

The production of pepsin and the release of stomach acid are increased by motilin [3]. While it has no effect on the contraction of the esophagus, motilin increases LES pressure by acting on preganglionic cholinergic neurons to produce acetylcholine, which in turn stimulates more cholinergic neurons feeding the LES's circular muscle. The quantity of stomach and lower esophageal sphincter contractions, as well as the level of motilin, are directly correlated with one another [5].

3. PREFERENTIAL ACTIVATION OF UPPER GASTROINTESTINAL NEURONAL FUNCTIONS

The capacity of motilin receptor agonists to induce enteric cholinergic activity is a key factor in their capacity to increase gastric emptying. Atropine inhibited the propulsive activity in healthy volunteers induced by a modest dose of erythromycin (40 mg), but a greater dose (200 mg) induced a non-propulsive, atropine-insensitive excitatory activity [6]. Furthermore, in the isolated stomachs of people and rabbits, modest doses of erythromycin, motilin, and the selective motilin receptor agonist GSK962040 markedly increased electrically evoked, cholinergically driven contractions [7, 8], whereas higher concentrations directly contracted the muscle. Repeated treatment with modest doses of erythromycin is thought to enhance gastric emptying, whereas higher doses cause nausea and stomach cramps due to a differential effect on the cholinergic and muscular activities of the stomach [9]. Similar to this, a direct contractile activity on the muscle may be consistent with erythromycin's capacity to promote meal-induced satiety in relatively high dosages [10].

The enhancement of cholinergic activity is clearly the principal therapeutic effect of motilin receptor agonists, despite broad motilin receptor antibody staining over the muscle layers of the upper GI tract appearing to contradict this conclusion. The identification of motilin receptor binding sites and antibody staining throughout the myenteric plexus support this hypothesis. The latter finding suggests that motilin may function differently in this muscle than it does in the myenteric plexus [11, 12]. This is because we have receptor numbers and function, so the difference must be occasioned by the density of receptors and the efficiency with which they bind the effector mechanism. Moreover, motilin receptor agonists are capable of impacting upper gastrointestinal functions, excluding the known effects owing to the fact that they stimulate the vagus nerve directly [13, 14].

4. LONG-LASTING EFFECTS AND DESENSITIZATION OF MOTILIN RECEPTORS

The intracellular transduction mechanism of the motilin receptor was first discovered through research on rabbit native tissue. Depoortere and Peeters (1995) reported that the release of calcium from intracellular calcium reserves through Gq-mediated inositol phosphate turnover was the mechanism by which activation of the motilin receptor raised intracellular calcium levels. However, subcellular motilin receptor desensitization could be investigated with the introduction of recombinant systems. The failure of the motilin receptor agonist ABT229 to alleviate dyspepsia or gastroesophageal reflux disease symptoms prompted most of this study. The causes of this failure are unknown, although one possibility is that tachyphylaxis occurred, which may have been made worse by ABT229's 20-hour plasma half-life and b.i.d. dosing schedule. Prior animal studies have shown that extended exposure to ABT229 can cause desensitization. [15].

Motilin receptor agonist-dependent effects on Ca^{2+} signaling were first discovered in a study by Li JJ *et al*., providing evidence in support of the theory that a medication with unique agonist-induced intracellular trafficking could prevent the loss of effectiveness with repeated doses [16]. In this work, motilin receptor-expressing cells were treated with motilin receptor agonists at doses ranging from 1 to 50 EC50, with administration at 100 EC50 resulting in the largest percent Ca^{2+} response.In these circumstances, washout responses to erythromycin and motilin recovered fully, but after the second drug exposure, ABT229 activity significantly decreased [17]. Despite having a 10-fold lower potency as a motilin receptor agonist, the data demonstrated that ABT229 was 10-fold more effective than motilin at causing desensitization. This result was connected to ABT229's particularly high capacity to promote receptor internalization [18]. Furthermore, whereas erythromycin and motilin phosphorylated receptors in a PKC-independent way, ABT229 had a higher propensity to do so. These findings suggest that drugs with a relatively low propensity to desensitize the motilin receptor might be better options and offer a potential explanation for why ABT229 failed in clinical trials. It is also believed that differences in agonist-induced desensitization among various m-opioid receptors are caused by phosphorylation by PKC rather than G-protein receptor kinases [19].

The aforementioned hypothesis had problems that were discovered in investigations with mitemcinal. In comparison to ABT229, this motilide was said to marginally worsen tachyphylaxis in rabbit duodenum muscle. In contrast, in CHO cells expressing the human motilin receptor, the desensitizing impact of mitemcinal was significantly less pronounced than that of ABT229 [20]. These findings demonstrate that the desensitization profiles of motilin receptor agonists can differ depending on the test. The translational significance of each of these *in vitro* trials must, therefore be viewed with caution because mitemcinal showed symptom alleviation in a fraction of diabetic gastroparesis patients [21]. The highly varied desensitization profiles created with motilin, erythromycin, and GSK962040 in isolated stomach preparations, which assess their capacity to promote cholinergically-mediated contractions, provide more evidence of the need for vigilance [11].

4.1. Endogenous Motilin Functions

It seems doubtful that eating will cause enough motilin to be released for it to have a meaningful impact on healthy volunteers' stomach motility. This theory seems to be supported by the finding that in healthy individuals, the motilin receptor antagonist RWJ-68023 had no effect on proximal gastric volume [21, 22]. The latter tests, however, should be handled

carefully because even high dosages of RWJ-68023 only completely block motilin's ability to constrict the stomach. However, it is plausible that changes in motilin availability in people with a variety of gut illnesses could influence their symptoms. For instance, functional dyspepsia and gastroesophageal reflux illness are linked to decreased motilin blood plasma concentrations. Additionally, the production of motilin was inversely associated with "indigestion symptoms" during a stressful interview [23].

It is interesting to note that left-sided abomasal displacement has been linked to a specific polymorphism of the motilin gene in dairy cattle (a single nucleotide altering a predicted transcription factor binding site) [24]. Bloating and the displacement of the abomasum from the abdominal wall are the first symptoms of this prevalent condition, which may also be partially inherited [3]. The abomasum's reduced motility, poor abomasal emptying, and poor cholinergic muscle responses are typically its precursors. The abomasal emptying rate is accelerated by erythromycin in cows after surgical LDA correction [25]. Together, these findings point to the necessity of more research into a putative relationship between endogenous motilin and defective stomach motility [26].

4.2. Structure of Motilin

Motilin is a 22-amino acid peptide hormone with a unique structure featuring a cyclic disulfide bond between two cysteine residues. It is part of the motilin family of peptides and plays a crucial role in regulating gastrointestinal motility by binding to motilin receptors on enteric neurons, enhancing gastric emptying (Fig. **1**) [3].

4.3. Mechanism of Motilin

Motilin is a gastrointestinal hormone that plays a key role in regulating gastrointestinal motility, especially during fasting. It is secreted by specialized M cells in the stomach and duodenum [27-29]. Motilin activates Motilin Receptors (MTLR), which are G protein-coupled receptors on smooth muscle cells and enteric neurons. This activation increases cyclic AMP (cAMP), leading to smooth muscle contraction [30]. It stimulates the Migrating Motor Complex (MMC), a pattern of muscle activity that clears the stomach and small intestine between meals. Motilin's action enhances gastric emptying, promotes peristalsis, and regulates digestive motility, ensuring efficient food transit (Fig. **2**) [31, 32].

4.4. Pathophysiology of Motilin

Disturbed gastric motility has been linked to motilin. According to a study, there is a considerable decrease in motilin levels during pregnancy. One week after delivery, the motilin level was back to normal. This phenomenon can be used to partially explain why gastrointestinal hypomotility occurs in pregnant people (Fig. **3**). Constipation, heartburn, and gallbladder stasis are among the symptoms of gastrointestinal hypomotility in pregnant women [33].

5. CLINICAL SIGNIFICANCE OF MOTILIN

5.1. Erythromycin: Clinical Use as a Motilin Receptor Agonist

The G protein-coupled receptors known as motilin receptors are activated by erythromycin. The name motilides is given to these substances. Erythromycin usage can greatly speed up gastric emptying by causing concentration-dependent stomach spasms. Erythromycin, however, is less effective than motilin [5, 34]. The motilin receptor agonist erythromycin makes people feel hungrier. Given their prokinetic impact, small-molecule motilin receptor agonists are of particular interest in the drug discovery process as well as motilides. This could lead to the development of more targeted treatments for diabetic gastroparesis [30, 35].

A study of people who had choledochotomy and cholecystectomy and received T tubes looked into duodenal-biliary reflux. The levels of motilin were measured in patients who had received a T tube following choledochotomy and cholecystectomy. The researchers divided the patients into two groups: one for reflux and the other for control. Compared to patients in the control group, individuals in the reflux group had significantly lower levels of motilin. This discovery could be useful in determining the cause of duodenal-biliary reflux. When the amount of motilin in the sphincter of Oddi decreases, it becomes hypomotile [36, 37].

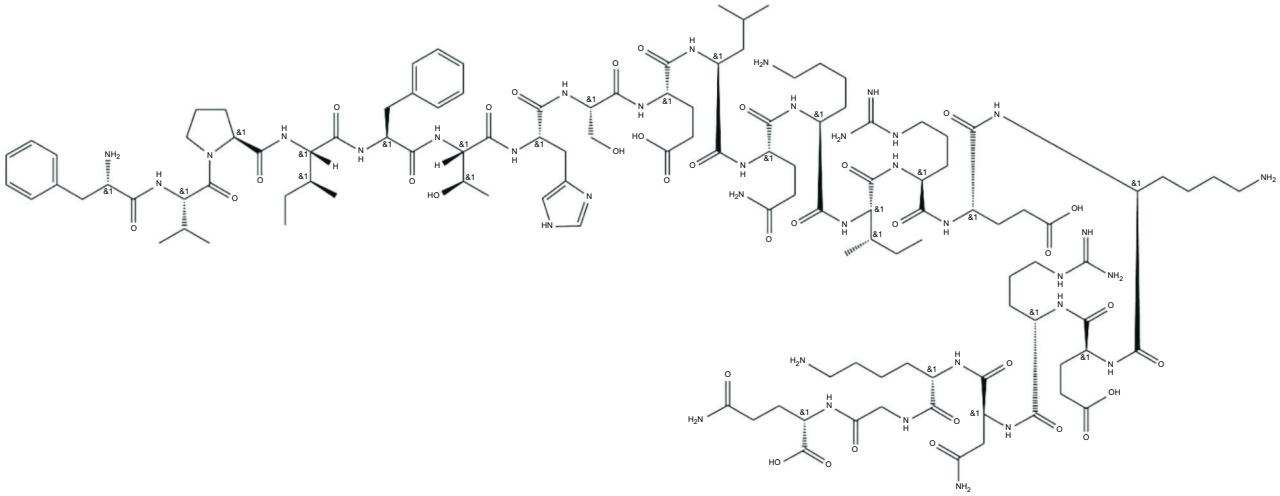
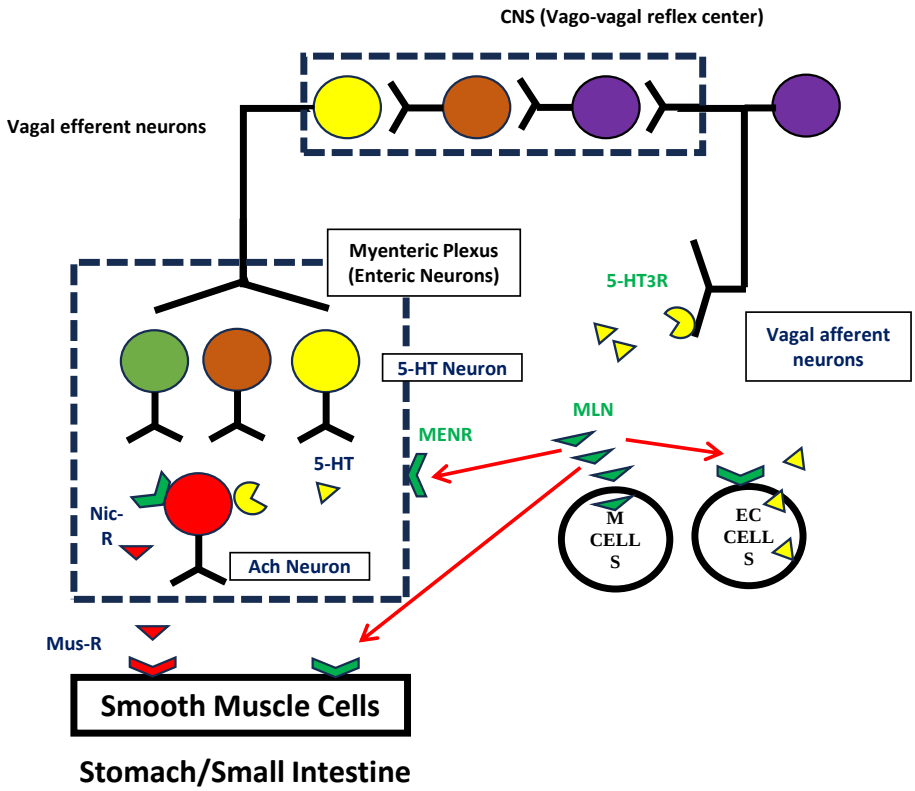


Fig. (1). Structure of motilin. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

(a)



(b)

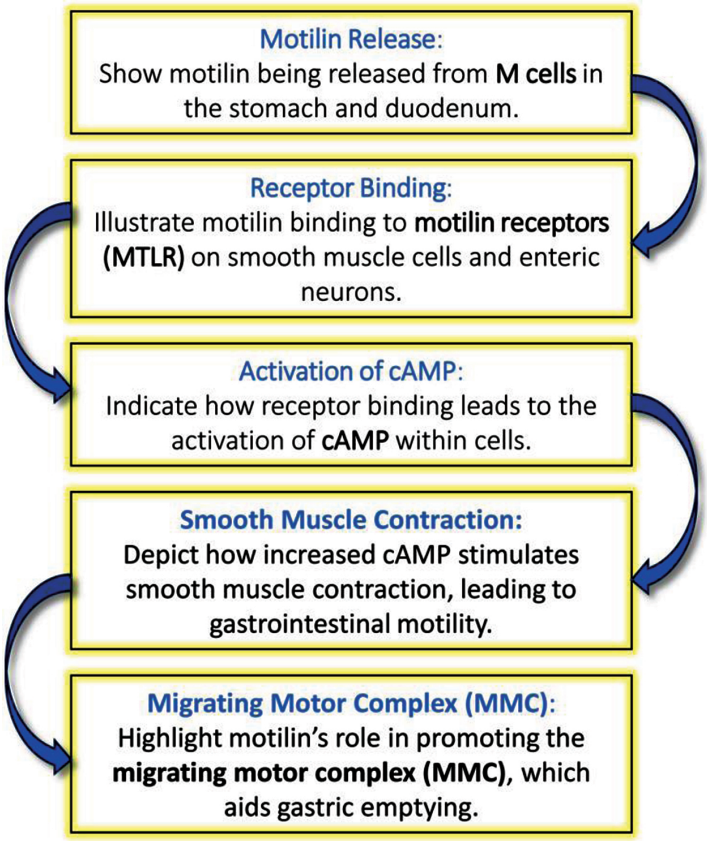


Fig. (2). (**a** and **b**) Mechanism of motilin. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

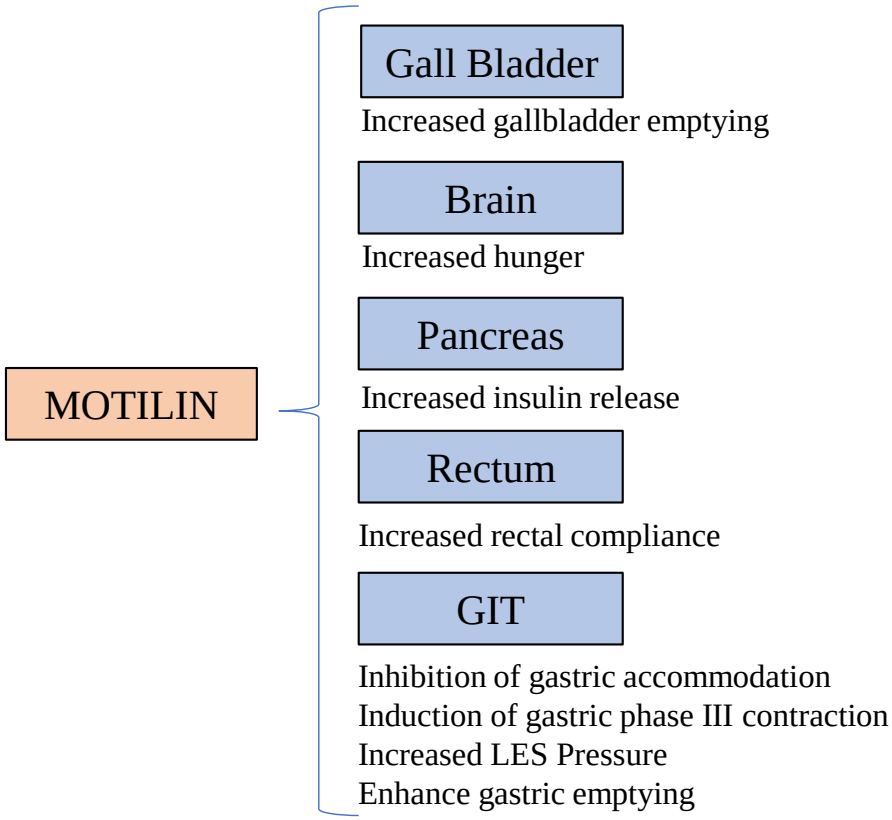


Fig. (3). Pathophysiology of motilin. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

5.2. New Motilin Receptor Agonists as Potential Drugs

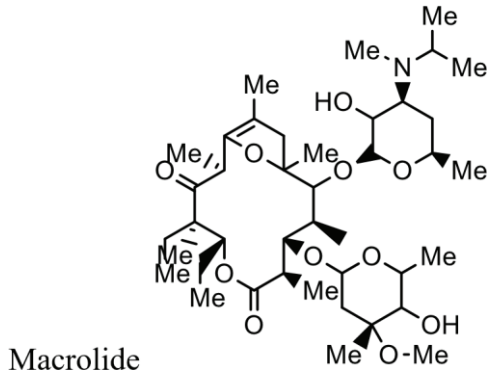
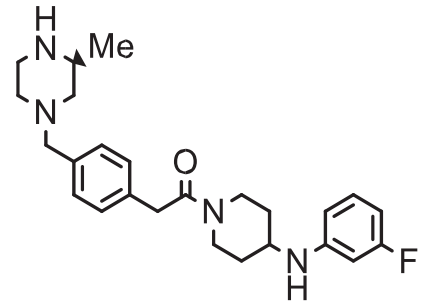
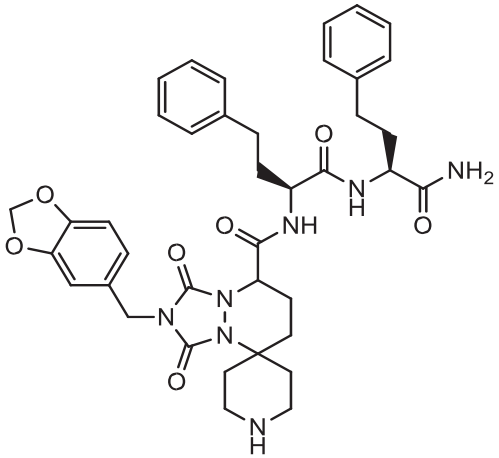
ABT229 is one of many motilin receptor agonists that were created from the 'macrolide' structure of erythromycin (a large macrocyclic lactone ring to which deoxy sugars are attached). These compounds are also referred to as 'motilides' because of their capacity to activate the motilin receptor. The majority, however, have fallen short for a variety of reasons (Motilin receptor desensitization and long-lasting actions" for discussion on probable desensitization) [26]. The capacity of ABT229 to exert activity in rats, a species in which a functioning motilin receptor has not been identified, serves as an example of the difficulties in discovering structure-activity connections for such complex compounds, including obtaining selectivity of action [38, 39].

It is critical to consider why motilin receptor agonists have not been successful in clinical development thus far. A list of compounds that are purportedly now under development may be found in Table **1**. Apart from the lack of studies guaranteeing the molecule is not a partial agonist at the native receptor expressed by the cholinergic nerves of the human stomach and/or does not fully behave like motilin (which has only a temporary ability to facilitate gastric cholinergic activity), the most obvious reasons for failure have to do with selecting the appropriate patient population and dosage of medication [40]. In the case of motilin receptor agonists, the latter aspect is critical because of the stimulation of stomach emptying to the point of nausea and development of tolerance with repeated use following high dosing. This is well illustrated by the fact that the use of ABT229 has been noted not to have the desired clinical success, while the different doses of erythromycin all have different outcomes. In a recent study, healthy volunteers showed acceptable GI tolerance to GSK962040, a small molecule motilin receptor that is well acknowledged with the ability to maintain human gastric cholinergic activity for several hours [11, 41], while speeding stomach emptying with a favorable pharmacokinetic profile. The time to maximum concentration was 0.5-2.8 h, and the elimination half-life was 25.6 h. As a result, when administered orally, it demonstrated dose-proportional serum concentration levels unaffected by food. These findings point to suitability as an oral medicine taken once daily. In a different investigation, the capacity of GSK962040 to promote stomach emptying persisted across a 14-day repeat-dose trial [42].

5.3. Clinical Use & Future Possible Applications of Motilin

The pharmaceutical prodrugs of motilin and its receptor agonists can have potential value in the treatment of gastrointestinal motility disorders. Clinically, motilin has been considered for gastroparesis, postoperative ileus, and functional constipation because it has been described to stimulate motility and facilitate gastric emptying. In the future, Motilin-based therapies can be a solution for obesity ,hunger, and satiety regulation as well as a solution for IBS, particularly the constipation-predominant IBS. Furthermore, motilin could be incorporated into other complex management with different GI affections, enhancing the efficacy in motility aberrations pathology.

Table 1. Motilin receptor agonists for management of abnormalities associated with delayed gastric emptying.

Compound	Structure	Profile	Clinical Data
Mitemcinal (GM-611)	 Macrolide	Mimicked the short-lived constriction of the duodenum in rabbits caused by motilin. Characterized *in vivo* using a variety of animal models [20].	Better gastric emptying and symptoms reduction were noted after three months in some patients with diabetic gastroparesis and BMI less than 35 kg/m², with T1DM, and well-controlled hyperglycemia [43].
GSK962040	 Small molecule	Recombinant receptor data translated from studies using isolated human and rabbit stomach tissues show sustained enhancement of motor nerve activity [44].	Enhanced gastric emptying was sustained through 14 days of repeated dosing in both healthy volunteers and patients diagnosed with type 1 diabetes mellitus and gastroparesis.
BMS591348	 Small molecule/peptide hybrid	Determined to be an agonist by detecting intracellular calcium increases using recombinant human receptors and by the use of a cell-based tachyphylaxis test, it was shown to have a favorable desensitization profile.	None available
RQ00201894	Small molecule; structure not yet disclosed.	Active at the human recombinant receptor and increased gastric emptying in dogs.	None available

CONCLUSION

The most obvious lessons for a translational pharmacologist are to not overly rely on artificial systems (like recombinant receptors produced in host cells) and on structural data (like immunohistochemistry) to determine a target protein's functions. Furthermore, the phrase "translational science" suggests that information is ultimately transferred to people, and during this process, a disproportionate emphasis on animal studies might occasionally result in results that are not appropriate. The evolving neuropharmacology of motilin serves as an example for each of these topics. Studies have focused on the specific ligand-dependent, long- and short-term capacities of motilin receptor agonists to promote stomach cholinergic activity. The capacity of medications and substances like erythromycin and GSK962040 to enhance gastric emptying of meals over extended durations of repeated dosage, as well as the ability of motilin to stimulate phase III MMC activity during fasting, is likely based on these activities.

There is currently enough evidence to indicate endogenous motilin participation in phase III of the MMC during fasting. Nevertheless, endogenous motilin has yet to be clearly implicated in the pathophysiology of GI disorders. Careful medication, dose, and patient selection are necessary for effectiveness when using motilin receptor agonists where concerns about receptor or functional desensitization are present.

AUTHORS' CONTRIBUTIONS

S., A.K.G., H.K. and A.K. contributed to the research design and implementation, as well as the data analysis and manuscript writing.

ABBREVIATIONS

MMC = Migrating Motor Complex

MTLR = Motilin Receptors

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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