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Journal of Drug Design and Research

Research Article

Metoclopramide: A Template for Drug Discovery

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Submitted: 20 October 2016

Accepted: 16 December 2016

Published: 02 January 2017

ISSN: 2379-089X

Keywords

- Metoclopramide
- Dopamine D2 receptor
- 5-HT4 receptor
- 5-HT3 receptor
- Drug discovery
- Emesis

Abstract

Metoclopramide was described in 1964 as an anti-emetic drug and stimulant of gastrointestinal motility. Dopamine D_2 receptor antagonism explained the anti-emetic activity and was suggested to stimulate gastrointestinal motility. An important use of metoclopramide and other D_2 receptor antagonists is to inhibit emesis caused by anti-cancer chemo radiotherapy. However, the use of new platinum-based anti-cancer drugs led to debilitating emesis, lasting for days and sometimes leading to refusal of treatment. Unlike conventional doses, higher doses of metoclopramide inhibited this severe emesis whereas subsequent trials with higher doses of other D_2 receptor antagonists were unsuccessful. Studies using ferrets replicated these findings and then demonstrated the ability of 5-HT_3 receptor antagonists to inhibit cisplatin-induced emesis, correlating with the known ability of higher concentrations of metoclopramide to antagonise at this receptor. Around the same time, the mechanism by which metoclopramide stimulates GI motility was shown to be independent of D_2 and 5-HT_3 receptor antagonism. A 'myenteric 5-HT-like receptor' was proposed, mediating the ability of metoclopramide to facilitate GI cholinergic activity. Later, this was characterised as the 5-HT_4 receptor. Extensive drug discovery followed the unravelling of the biology of metoclopramide. The serendipitous discovery of this drug has therefore contributed to development of three new drug classes: selective (peripherally-restricted) antagonists at D_2 and 5-HT_3 receptors and selective agonists at the 5-HT_4 receptor. The latter are used to treat idiopathic constipation. 5-HT_3 receptor antagonists, together with dexamethasone and if necessary, NK_1 receptor antagonists, prevent moderate-to-severe emesis during anti-cancer treatment and hence, began a revolution in cancer patient care. The ability of 5-HT_3 receptor antagonists to cause mild constipation was used to treat diarrhoea-predominant irritable bowel syndrome, achieving clinical success but later associated with severe adverse events. Antagonists at the D_2 receptor treat mild forms of emesis. Metoclopramide is still used as a gastric prokinetic and anti-emetic drug.

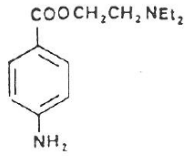
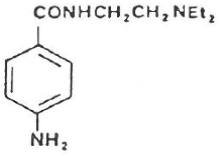
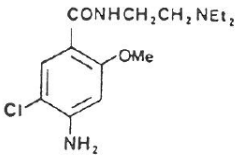
INTRODUCTION

Metoclopramide was synthesised during a programme aimed at improving on the properties of procainamide, a cardiac anti-arrhythmic and local anaesthetic drug which was itself derived from procaine (conversion of the ester to the amide linking the benzamide ring and the side chain of procaine gave procainamide, resistant to breakdown by esterases). Further substitution of the benzene ring created metoclopramide, a compound with surprising anti-emetic properties [1-3] (Table).

Unlike procainamide, metoclopramide had negligible local anaesthetic or cardiac anti-arrhythmic activity [4]. Anti-emetic activity was demonstrated against different emetic stimuli, including apomorphine, a dopamine receptor agonist [5]. Subsequently, metoclopramide was found to increase gastrointestinal (GI) motility and reduce symptoms associated with various upper GI disorders [6]. At the time the mechanisms of these actions were unclear, but it was known that the drug could act as a dopamine receptor antagonist [1,7]. Later, as dopamine receptors were defined, metoclopramide was shown to be a D_2 receptor antagonist, eventually proven to be selective over the D_3 receptor and the α_1-adrenoceptor [8,9].The drug found widespread use as an anti-emetic (e.g. during post-operative care or for patients with gastritis, migraine, dysmenorrhoea and drug- or treatment-induced forms of emesis including that caused by anaesthesia, radiation and/ or chemotherapy for treatment of cancer) and as a stimulant of upper gut motility (e.g. for patients with gastro-esophageal reflux disease, gastroparesis and functional dyspepsia) [10,11]. There are now many generic versions of metoclopramide across the world.

The ability to antagonise at D_2 receptors has beneficial and adverse consequences.

1. Metoclopramide blocks D_2 receptor-mediated functions within the area postrema (AP), a highly vascularised circumventricular organ of the brain at the caudal

Procaine	Procainamide	Metoclopramide
		
from the ester link to the amide further substitution of the benzene ring		

extremity of the floor of the fourth ventricle. It is outside the blood brain barrier, so it can be stimulated by emetogenic substances in the blood (eg. toxins, drugs) to initiate vomiting; the AP is therefore described as a "chemoreceptor trigger zone" [12]. Surprisingly, the source of dopamine which activates D_2 (and also D_3) receptors to initiate vomiting is not clear [12]. Nevertheless, by antagonising D_2 receptors within the AP drugs such as metoclopramide exert anti-emetic activity.

2. Metoclopramide also blocks D_2 receptors in the pineal gland, again outside the blood-brain barrier, increasing release of prolactin. Prolactinaemia is therefore a side-effect.

3. The ability of metoclopramide to cross the blood-brain barrier means that D_2 receptor antagonism occurs at striatal areas involved in control of movement. As a result, the drug is associated with tardive dyskinesia (involuntary, repetitive movements of the extremities or facial areas) [13]. In 2009 the FDA required a black box warning to be added to the label [14].

4. Metoclopramide can block the inhibitory actions of D_2 receptors within the GI tract, originally proposed as a mechanism by which gastric emptying is increased [1,7]. However, exactly when these receptors are activated and whether-or-not they have a true pathological role remains controversial [12,15,16] and will be discussed below.

Many attempts were made to identify D_2 receptor antagonists with little or no ability to cross the blood brain barrier. The most successful was domperidone, developed in 1974 from pimozide, a butyrophenone [17]. This drug is sold in many countries as an antiemetic, gastro prokinetic agent, and galactogogue (to increase lactation), although domperidone is not registered for use within the USA (the FDA required large clinical trials to better ascertain efficacy and safety) [18,19]. Concerns about the cardiac safety of domperidone surfaced in the early to mid-1980s with reports of cardiac arrest, ventricular arrhythmias, and sudden death associated with use of the intravenous domperidone (since withdrawn from the market). Oral domperidone has also been associated with an increased likelihood of ventricular arrhythmia, especially at higher doses or when given with other drugs acting as CYP 3A4 inhibitors [18,20].

Domperidone is also an α_1-adrenoceptor antagonist [21-23] and in contrast to metoclopramide (discussed below) does not increase cholinergic activity in human isolated stomach [24,25] at concentrations which bind to human D_2 receptors [26]. The latter is consistent with the idea that domperidone acts indirectly, in a disease-specific manner, to increase gastric emptying. Thus, the drug does not change gastric emptying in healthy volunteers but may increase gastric emptying and improve symptoms in patients with gastroparesis or Parkinson's disease (some caution is suggested by the lack of control arms in many of the positive studies) [25,27]. Such disease-dependency could involve antagonism of an inhibitory activity of dopamine in the stomach, although this has not been demonstrated for endogenous dopamine [16]. Alternately, D_2 antagonism will occur in the AP, inhibiting nausea and vomiting, and thereby overcoming an associated delay in gastric emptying [12,15].

Understanding the mechanism of action of domperidone has relevance in helping to unravel the initial hypothesis that metoclopramide was only a D_2 receptor antagonist.

5-HT receptors

It became clear that metoclopramide could also interact with 5-HT receptors which were, at the time, poorly understood. The process of 5-HT receptor definition began in 1957 when Gaddum & Picarelli [28] published their experiments with guinea-pig ileum. They defined an M receptor (neuronally-mediated muscle contractions, blocked by morphine and also by atropine, cocaine, and methadone, even after dibenzyline) and a D receptor (non-neuronally-mediated smooth muscle contractions, blocked by dibenzyline and also by lysergic acid diethylamide, dihydroergotamine and 5-benzyloxygramine, even after morphine). In 1986 the classification was updated and three receptors were defined: 5-HT_2 (the old 5-HT D), 5-HT_3 (5-HT M) and a tentative (later confirmed) '5-HT_1-like' receptor which had similarities with a heterogeneous group of 5-HT_1 (high affinity) binding sites [29]. Today, seven different 5-HT receptors have been cloned and characterised, with several subtypes for some of the receptors. All are G protein-coupled, seven transmembrane receptors except 5-HT_3, which is a cation channel with potentially heterogeneous subunits (5-HT_3A-E [30]). One 5-HT_4 receptor has been characterised but several C-terminal splice variants exist [31].

Metoclopramide and the 5-HT M or 5-HT_3 receptor

Metoclopramide was found to antagonise a neuronally-mediated action of 5-HT in guinea-pig isolated colon [32] and ileum [33-35], defining the molecule as a 5-HT M receptor antagonist. Later experiments demonstrated that metoclopramide could also antagonise other neuronally-mediated actions of 5-HT in the peripheral nervous system (notably, 5-HT-evoked tachycardia in rabbit isolated heart or bradycardia in anaesthetised rats

(the von Bezold-Jarisch reflex)) [35,36]. Fozard and colleagues subsequently showed that (-)-cocaine and structurally-related compounds also antagonised these actions of 5-HT, knowledge which led to the synthesis of MDL72222, the first selective 5-HT_3 receptor antagonist, originally aimed at the treatment of migraine [37].

The 'myenteric 5-HT-like receptor'or 5-HT_4 receptor

At around the time the 5-HT_3 receptor was being characterised it became clear that D_2 receptor antagonism could not explain how metoclopramide increased GI motility [38]. Instead, it was argued that metoclopramide acted on cholinergic nerves within the GI enteric nervous system (ENS), but not necessarily on cholinergic neurons outside the ENS. This activity was independent of brain function (not prevented by vagotomy and observed in isolated GI tissues). Experiments *in vitro*, including human stomach, showed that metoclopramide facilitated on-going cholinergic activity evoked by stimuli such as electrical field stimulation, facilitating the release of ACh rather than directly stimulating muscarinic receptors [24,38,39,40,41]. This activity was not due to antagonism at pre-junctional muscarinic receptors, was not blocked by antagonists at α or ß adrenoceptors or at D_2 receptors, or by antagonists at various other receptors and mechanisms [40]. Instead, relatively high concentrations of 5-HT mimicked the response [42] and non-selective ligands at 5-HT receptors mimicked or blocked this action of metoclopramide [40,41]; the notable exception was the failure to mimic or inhibit this activity of metoclopramide with a 5-HT_3 receptor antagonist, leading to the proposal that metoclopramide facilitated cholinergic activity within the ENS by activating a 'myenteric 5-HT-like receptor' [41]. This quickly became defined as the 5-HT_4 receptor (see below).

In 1988 Bockaert and colleagues [43] identified a 'non-classical' 5-HT receptor in mouse embryo colliculi neurons and in guinea pig hippocampal membranes, which when activated increased adenylate cyclase activity. Relatively high concentrations of ICS 205-930, a 5-HT_3 antagonist at low concentrations, competitively antagonised the response and the authors suggested 5-HT_4 as the name for this new receptor, later accepted as part of the 5-HT receptor nomenclature [44]. Further work showed that metoclopramide and other substituted benzamides, including renzapride (BRL 24924), were 5-HT_4 receptor agonists [45]. Returning to the guinea-pig ileum, Craig and Clarke [46] demonstrated that 5-HT and renzapride each facilitated the peristaltic reflex by a mechanism blocked by a relatively high concentration of ICS 205-930, but not by the 5-HT_3 receptor antagonist ondansetron, suggesting that the prokinetic action of renzapride and 5-HTwere mediated via 5-HT_4 receptor activation.

Involvement of the 5-HT_3 receptor in nausea and vomiting

The introduction of new anti-cancer treatments, such as the platinum-based drugs, were found to be associated with severe forms of nausea and vomiting, potentially lasting for days and sometimes leading to refusal of further treatment; conventional doses of existing anti-emetic drugs, including metoclopramide, were poorly effective. In 1981, high intravenous doses of metoclopramide were shown to reduce emesis in patients receiving cisplatin for treatment of cancer, contrasting with the poor effectiveness of prochlorperazine [47]. Later trials failed to replicate this activity with high doses of the D_2 receptor antagonists domperidone or alizapride [48,49]. Thus, it seemed unlikely that high doses of metoclopramide achieved greater anti-emetic activity simply because the drug somehow blocked D_2 receptors in the brain more effectively. This observation was confirmed and extended by use of a ferret model of emesis. In these experiments we were able to show that cisplatin-induced emesis was not affected by domperidone but was prevented by renzapride, a molecule with poor ability to antagonise at the D_2 receptor, good ability to activate the so-called 'myenteric 5-HT-like receptor' (5-HT_4) and potent ability to antagonise at the 5-HT_3 receptor [50-52]. Subsequent experiments with MDL72222 confirmed that this anti-emetic activity was due to 5-HT_3 receptor antagonism [53]. Our experiments, conducted within the laboratories of Beecham Pharmaceuticals (now part of GlaxoSmithKline), were then replicated using our own compound (the selective 5-HT_3 receptor antagonist BRL43694 or granisetron) and those from Glaxo (GR38032F or ondansetron; now part of GlaxoSmithKline) and Sandoz (ICS 205-930 or tropisetron; now part of Novartis), leading to the filing of a patent claiming the use of these compounds for treatment of emesis [54], successfully upheld over ondansetron. At the same time and following our original abstract highlighting the anti-emetic activity of renzapride [51], experiments to demonstrate the activity of the 5-HT_3 receptor antagonist ICS 205-930 [55] were swiftly sponsored by Sandoz, the manufacturer of ICS 205-930 (B.P. Richardson, personal communication). Away from the competitive industrial arena, there was now no doubt that the conclusions reached by our findings were consistent with the earlier observations that relatively high doses of metoclopramide antagonize 5-HT M (5-HT_3) receptors in the peripheral nervous system [35], now shown to be involved in the mechanisms of emesis.

5-HT_3 receptor antagonists prevent cytotoxic-associated vomiting by blocking the ability of 5-HT, released from mucosal enterochromaffin cells in the upper GI tract, to activate 5-HT_3 receptors on abdominal vagal nerve terminals and thereby effectively 'desensitise' the vagus to the pro-emetic stimulatory actions of 5-HT and other substances (e.g. prostanoids) released during the cytotoxic treatment [12]. Today, selective 5-HT_3 receptor antagonists (e.g. granisetron, ondansetron, tropisetron), combined with a corticosteroid such as dexamethasone, are the first-line treatment for patients receiving 'moderate-to-severe' emetogenic anti-cancer treatments. The addition of an NK_1 receptor antagonist for patients receiving 'highly emetogenic' treatments, further blocks vagal nerve activity and controls the 'acute' emesis (during the first 24h after initiation of treatment) and the 'delayed emesis' which can occur 24 - 48 h after treatment [56]. Together, this has revolutionised treatment of cancer and reduced health care costs [57,58]. Most recently, evidence is emerging that palonosetron, a long-lasting 5-HT_3 receptor antagonist, may provide additional control by a mechanism argued to involve further inhibition of substance P, NK_1 receptor-mediated responses via a unique interaction with the internalised

5-HT_3 receptor [59].

Selective 5-HT_4 receptor antagonism

Prucalopride, the first selective, clinically-available 5-HT_4 receptor agonist was described 35 years after the description of metoclopramide and 13 years after the first characterization of the 5-HT_4 receptor [60]. This followed numerous other non-selective 5-HT_4 receptor agonists, some of which made it into the clinic [31,61]. The list includes cisapride (also active at 5-HT_{2A}, 5-HT_{2B} and the α_1 adrenoceptor; withdrawn because of activity at the human Ether-a-go-go Related Gene (hERG) encoded K^+ channel), tegaserod (also a 5-HT_{2B} receptor antagonist, withdrawn because poor efficacy and possible association with ischaemic colitis did not justify the risk) and others such as clebopride and cinitapride. Notably, prucalopride is used in many countries for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. The use of prucalopride as a stimulant of gastric emptying (the original use for metoclopramide) has not yet been realised. In part, this may be due to the increasing realisation that although metoclopramide, an anti-emetic and gastric prokinetic drug, achieves some success in treating disorders such as gastroparesis (a disorder characterised by delayed gastric emptying [62]), a poor correlation between gastroparesis symptoms and slow gastric emptying [63] suggests the need to consider different types of treatment. Nevertheless, gastric prokinetic agents remain an important tool with which to facilitate the delivery of key orally-administered drugs out of the stomach and into the intestine for absorption, in, for example, patients with Parkinson's disease needing to improve the otherwise reduced absorption of L-dopa. Other selective 5-HT_4 receptor agonists (velusetrag or TD-5108, TD-8954, naronaprideor ATI-7505) have been described [64-66].

CONCLUSIONS

The serendipitous discovery of metoclopramide, its use as a therapeutic drug and research into its mechanisms of action has led to the discovery of three new classes of drug. This includes the development of selective (peripherally-restricted) D_2 receptor antagonists, selective 5-HT_4 receptor agonists and selective 5-HT_3 receptor antagonists. Further, this research directly led to the discovery of the anti-emetic activity of selective 5-HT_3 receptor antagonists and to a revolution in cancer patient care. Today, metoclopramide and drugs from each of these classes are in widespread clinical use.

ACKNOWLEDGEMENTS

GJS currently receives funding from The Dunhill Medical Trust, The research into ageing fund, set up and managed by AgeUK, the BBSRC (Case award with GlaxoSmithKline) and Takeda pharmaceuticals.

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Cite this article

Sanger GJ (2017) Metoclopramide: A Template for Drug Discovery. J Drug Des Res 4(1): 1031.