



Discovery and development of motilin agonists

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The incidental discovery at our laboratory that erythromycin (EM) greatly stimulates gastrointestinal (GI) contractile activity in conscious dogs prompted us to examine the mechanism of action of EM and EM was found to be a non-peptide motilin agonist. In collaboration with Dr. S. Omura, the Kitasato Institute of Tokyo, we examined the structure-activity relationship in more than 300 derivatives of EM, and found that the macrolide compounds which manifest motilin-like activity should be composed of a 14-membered lactone ring with desosamine (aminosugar) and cladinose (neutral sugar) attached at C5 and C3 with a glycoside linkage. A number of desosamine greatly affects motilin-like activity, and 8,9-anhydroerythromycin 6,9-hemiketal propargyl bromide (EM536), was the most potent motilin agonist among the derivatives, the activity of which is about 3000 times more than that of EMA. We have named macrolides with motilin activity motile to mean motilin-like macrolides.

In the study of receptor binding in human gastric tissue, EM574, which is one of the EM derivatives, and has been selected for clinical

use, specifically displaced ^{125}I -motilin bound to smooth muscle homogenates and has a K_d value of 7.8×10^{-9} M, compared with 4.5×10^{-9} M for motilin. Film autoradiograms show that ^{125}I -motilin-binding sites are localized in the muscle layers, and the labeling disappeared in the presence of a 1000 times molar concentration of EM574.

EM574 has now been proved to be effective in improving delayed gastric emptying in various diseases. In dog experiments, accelerating effect of EM523 on gastric emptying of solid-liquid meals has been demonstrated.

In the recent studies on stimulatory mechanism of EM523-induced contractions in postprandial stomach of conscious dogs, it was found that EM523, in doses 1-30 $\mu\text{g/kg-h}$, induced a dose-dependent increase in fed-type contractions. EM523-induced contractile activity was partially inhibited by atropine, hexamethonium, dopamine, 5-hydroxytryptamine 3 receptor antagonist, and substance P antagonist but soon recovered. Atropine-resistant and EM523 induced contractions were further inhibited by 5-HT₃ receptor antagonist and substance P antagonists, and the combined use of the two antagonists completely eliminated the atropine-resistant and EM523-induced contractions. EM523-induced contractions in the fed stomach are quite different from phase III contractions in the interdigestive state, and are mediated partially through the cholinergic pathways. The non-cholinergic pathways involve 5-HT₃ and neurokinin 1 receptors.

In addition to the action of motilides in the fed state, EM523 was found to stimulate the endogenous release of pancreatic polypeptide, insulin and glucagon as well as motilin, but not gastrin, CCK, secretin during the interdigestive state. The significant release of these hormones was suppressed by pretreatment with atropine and hexamethonium, and completely eliminated by 5-HT₃ receptor antagonist and truncal vagotomy. These findings suggest that EM523 stimulates the endogenous release of pancreatic polypeptide, insulin and motilin by activating the cholinergic parasympathetic nerve system, finally stimulating the endocrine pancreas through vagally cholinergic muscarinic receptors in the pancreatic islets.

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