9th seminar

Pharmacology of the gastrointestinal tract (ulcus therapy, prokinetic drugs)

László Drimba M.D.

University of Debrecen

Department of Pharmacology and Pharmacotherapy

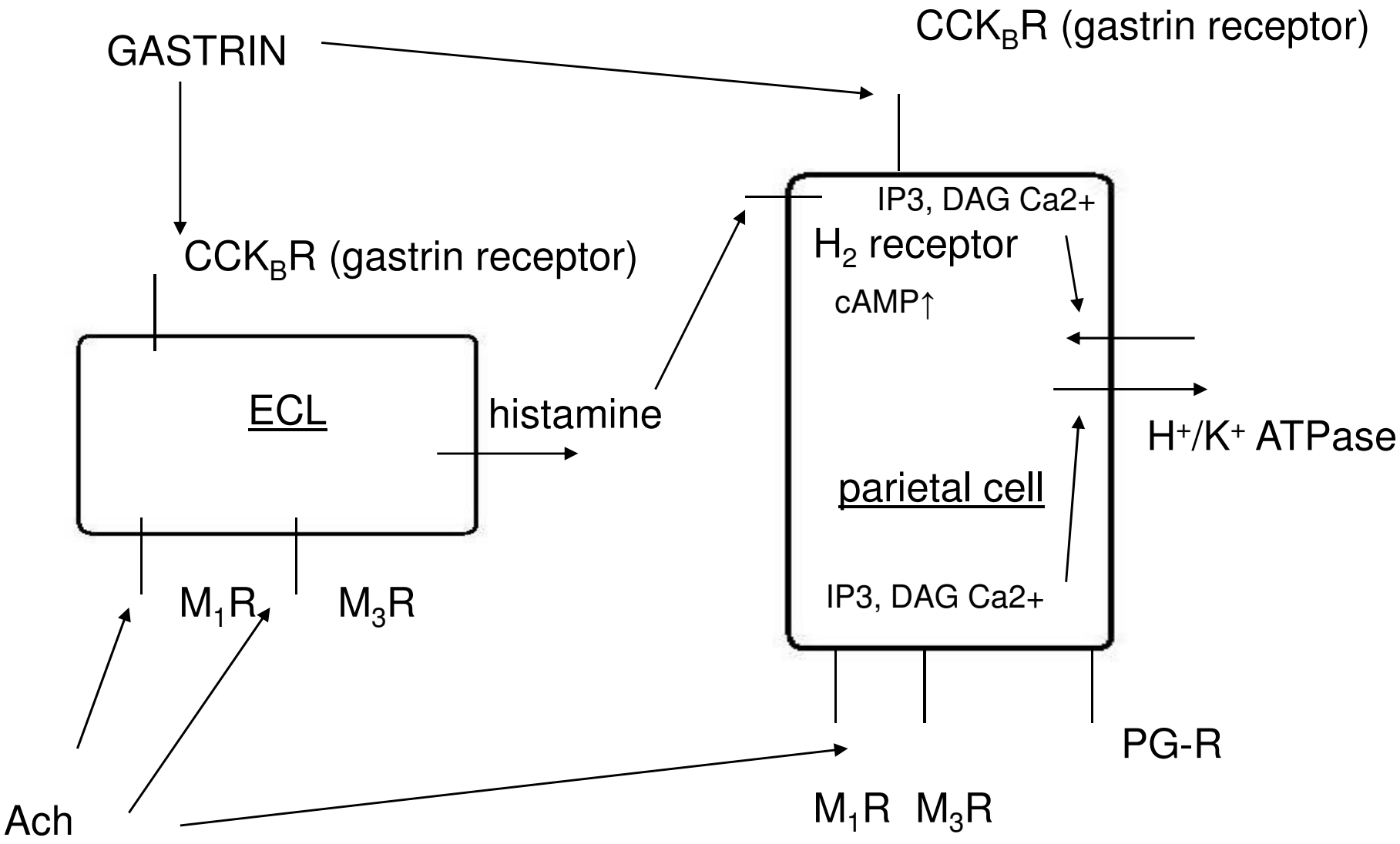
Gastric/duodenal ulcus

- ulcus ventriculi
- ulcus duodeni

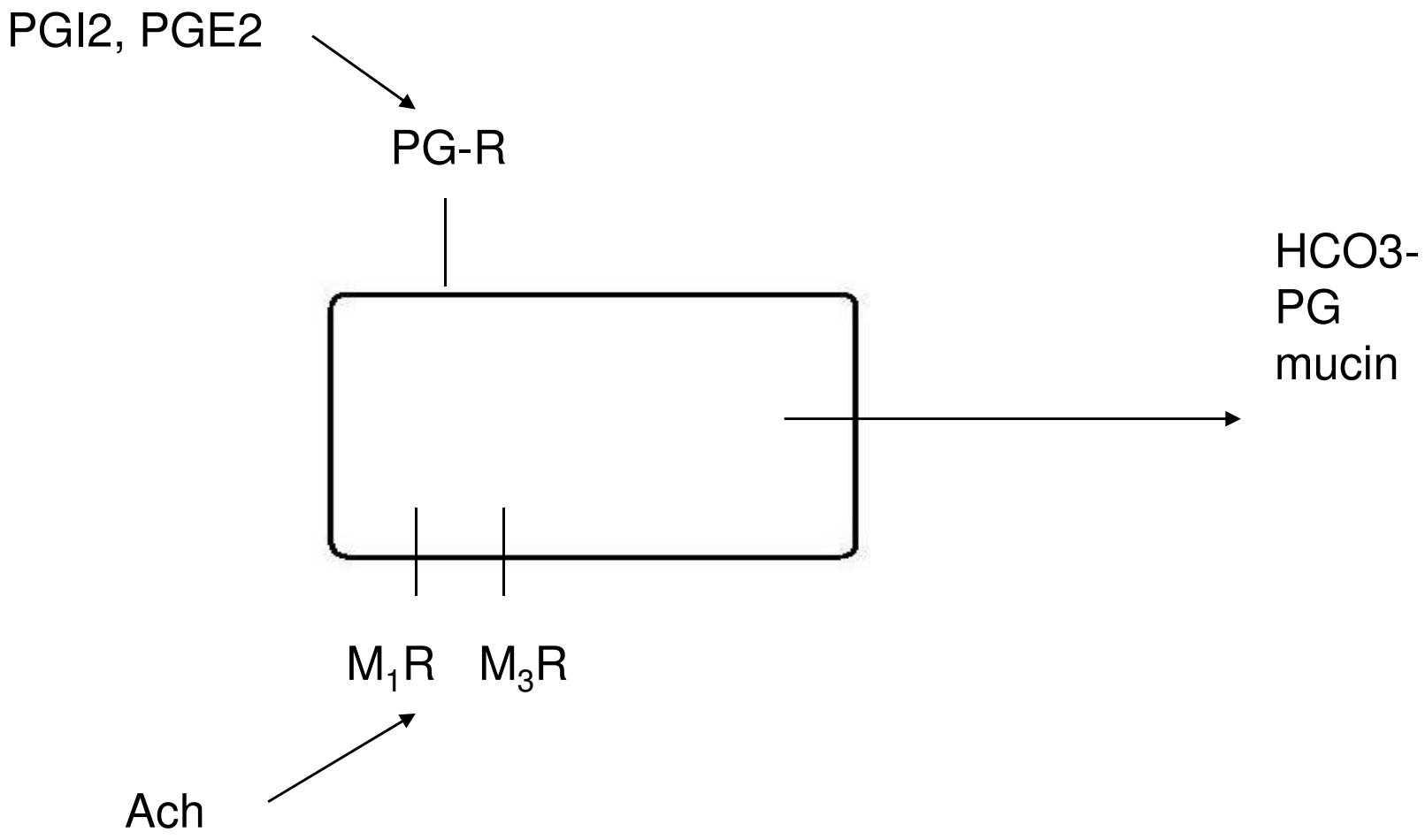
H+ secretion:

- neural → n. X. (Ach)
- endocrine → gastrin
- paracrine → histamine

gastric acid secretion



Mucous secretion



Gastric/duodenal ulcus

<u>agressive factors↑</u>

- HCl
- pepsine
- Helicobacter pylori!

<u>protective factors↓</u>

- mucin
- HCO3-
- PGs
- rapid cell proliferation

Therapeutic ways

- gastric acid secretion↓
  - proton pump inhibitors (PPI)
  - H_2R blocking drugs
  - cholinolytic agents
- neutralizing gastric acid
  - antacids
- defensive factors↑
  - sucralfat
  - PGR agonists
- anti Helicobacter pylori th.

gastric acid secretion↓

proton pump inhibitors (PPI)

- omeprazole, pantoprazole
- m.o.a.: Cys-SH covalent binding→irreversible!
- pro-drug (hydrolized by acid→active form)
- ↓ basal, postprandial H+ secretion
- popular!

- hypochlorhydria→bacterias↑
- compensatoric hypergastrinaemia→mucosa hyperpl.

- Th.:gastric ulcus (refracter), Zollinger-Ellison syndrome

gastric acid secretion↓

H_2R blocking drugs

- cimetidine, ranitidine, nizatidine:
  - selective H_2R blocker
  - inhibiting CYP3A4,

    prolactine ↑, oestrogen↑→impotency, gynecomastia

    BDZ metabolism↓→BDZ plasma level↑ →intoxication!
  - a.e.: coronary spasm
  - basal H+ secretion ↓
  - th.: GERD, gastric/duodenal ulcus, pre-op.
- famotidine

gastric acid secretion↓

cholinolytic agents

- M_1, M_3 receptor blocking
- pirenzepine - M_1 antagonism
- a.e.: cholinolytic symtomps

neutralizing gastric acid

antacids:

- $AlOH_3$
- $CaCO_3$
- $MgOH_2$
- $NaHCO_3$

alcalic pH

non-receptorial antagonism

systemic effect:→ electrolyte disturbances

defensive factors↑

sucralfate (Al-sucrose-sulfat)

- anionic, polimer structure in gastric pH
- ulcerated area - protein binding
- PG synthesis↑
- EGF activation

misoprostol (Cytotec®)

- PGE_1 analog
- agonism of PG-R→mucin, HCO3-↑
- th.: erosive gastritis induced by NSAIDs
- CI!.: pregnancy

anti Helicobacter pylori th.

- PPI
- metronidazole (Klion®)
- amoxicillin
- erythromycin
- tetracycline

Prokinetic agents

GERD:

- gastric ulcus
- oesophageal ulcus
- Barrett oesophagus
- carcinoma

- Th.: PPI, prokinetics

GIT motility (plexus submucosus, plexus myentericus)

- oral contraction: serotonin ($5HT_4$) triggered cholinerg (Ach) contraction (can be inhibited by dopamine-D_2)

- aboral relaxation: peptiderg relaxation (VIP, CGRP)

Prokinetic agents

$5HT_4$ agonism:

- cisapride (Coordinax®)
  - QT↑, VT (torsade de pointes)

D_2 antagonism:

- metoclopramide, domperidone
  - extrapyramidal disturb. (pseudo Parkinson disease)
  - galactorrhea (PIF)

Motiline R agonism:

- erythromycine (makrolide AB)
  - diarrhea