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10. DRUGS USED IN TREATMENT OF GASTROINTESTINAL DISEASES

10.1. DRUGS AFFECTING APPETITE

Satiety and hunger are regulated by the hypothalamus (fig. 10.1). Stimulation of a lateral hypothalamic area referred to as the hunger center leads to an increase in appetite, whereas inhibition of that center leads to food refusal. Experimental destruction of the satiety center in the medial hypothalamic area leads to unstoppable desire to devour food. The hunger and satiety centers represent an aggregate of functionally interrelated structures of the central nervous system; they regulate food behavior and coordinate the gastrointestinal function. The hunger center activity is controlled by noradrenergic neurons, whereas the satiety center activity is controlled by serotonergic neurons. Stimulation of the noradrenergic system of the brain results in suppression of the hunger center and in an increase in appetite, whereas stimulation of the serotonergic system results in activation of the satiety center and, consequently, in reduced appetite.

Along with this, there is humoral regulation of food intake which involves hormones ghrelin and leptin. Ghrelin is a peptide hormone produced by cells of the gastrointestinal tract; the concentration of this hormone increases uponfasting and decreases after food intake. This hormone regulates appetite; its high blood concentration leads to greater food intake and weight gain. On the other hand, once weight gain has occurred, ghrelin blood concentration decreases, and, consequently, weight loss occurs. Thus, ghrelin is supposedly involved in body weight regulation. Receptors tothis hormone are found in the ventromedial hypothalamic region and arcuate nucleus. These receptors are involved in regulation of releasing hormone production, appetite increase, changes in blood glucose levels, changes in lipid metabolism, regulation of secretion and peristalsis proceeding in the walls of the gastrointestinal tract.

Leptin is another appetite influencing hormone which is synthetized by adipocytes. Leptin has an anorexigenic effect, i.e. its increased blood concentration leads to a decreased appetite. Leptin receptors are found in the hypothalamus. Leptin stimulates the sympathetic nervous system, thus increasing arterial pressure, heart rate, and enhancing thermogenesis. Leptin is involved in regulation of energy metabolism and body weight. It acts via hypothalamic receptors to inhibit the synthesis and release of neuropeptide Y, which causes hunger, and, therefore, it is often referred to as the satiety hormone. In physiological environment, leptin inhibits the synthesis of insulin; insulin, exerting an effect on adipose tissue, stimulates the production of leptin; therefore, leptin is regarded as one of the factors involved in pathogenesis of diabetes mellitus type 2.

Moreover, insulin influences appetite as well. Insulin is a hormone secreted by pancreatic cells (fig. 10.1). Secretion of insulin into the blood leads to an increased transport of glucose through cellular membranes of myocytes and adipocytes; as a result, the blood glucose concentration goes down. Deviations in blood glucose concentration from a constant level are perceived by hypothalamic glucoreceptors and cause activation of the hunger center (fig. 10.1).

Table 10.1. Drugs influencing appetite can be divided into the following two groups

1. Appetite stimulants	2. Appetite suppressants (anorexigenic agents)
Bitters Essential oils Anamorelin℘ Megestrol Dronabinol℘	Liraglutide Lorcaserin℘ Sibutramine Fluoxetine

Appetite Stimulants

Bitters (***amara***) include plant-based medicines containing bitter tasting glycosides: sweet flag root, dandelion root, *Artemisia absinthium* extract, and *Achillea millefolium* herb. Bitters irritate the taste buds of the oral mucous membrane. Their effect is felt right before meals and during meals, so these medications are administered to patients with decreased appetite and should be taken 15–20 minutes before meals. Bitters are contraindicated for patients with hyperacidic gastritis.

Medicines containing essential oils of melissa, peppermint, fennel, nutmeg, cloves, thyme, pine needles, anise, salvia, cinnamon, and lavender. Essential oils irritate the taste buds of the oral mucous membrane and reflexively promote excitability of the hunger center; the meal that follows is accompanied by increased secretion in the stomach.

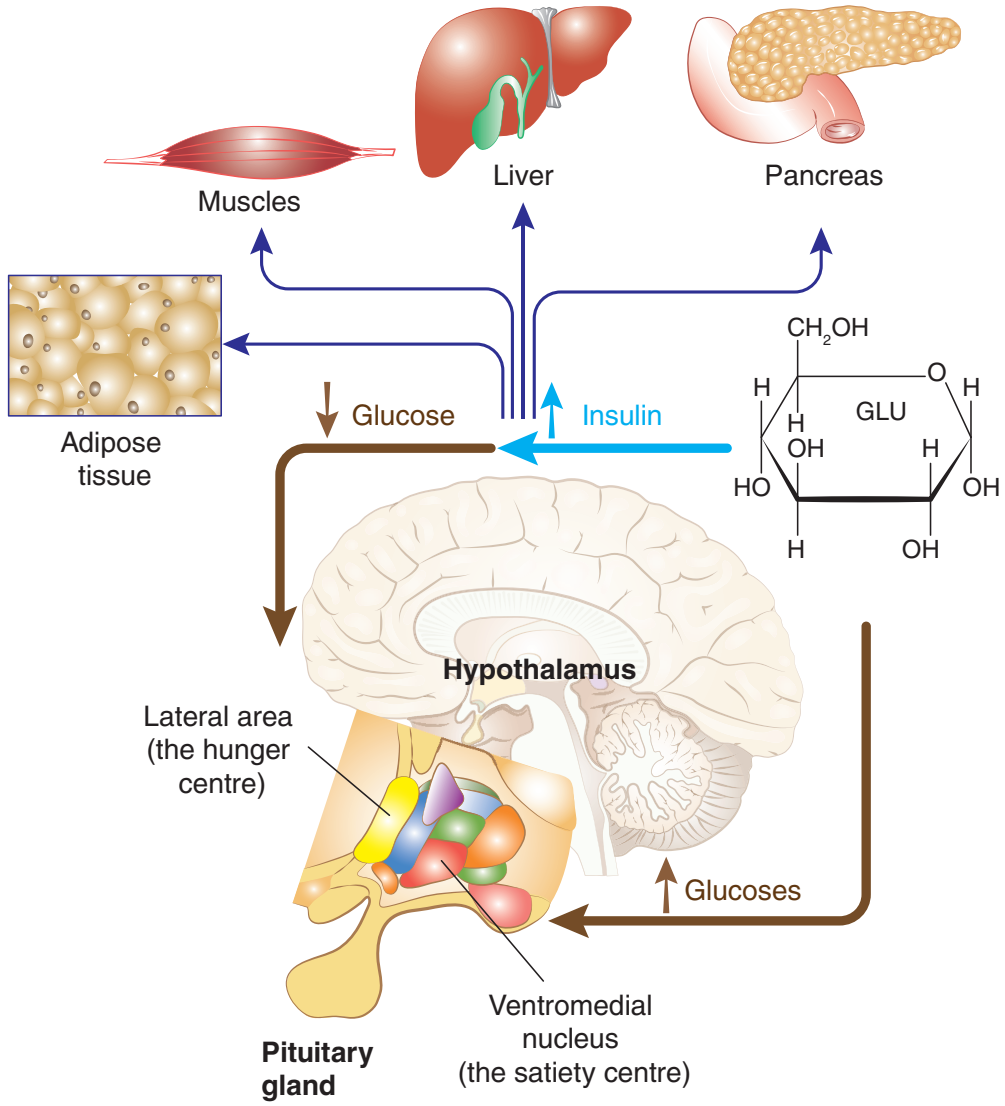

Fig. 10.1. Neurohumoral regulation of appetite

Anamorelin℗ is a selective ghrelin receptor agonist — the hunger hormone — secreted in the stomach. It increases the plasma levels of growth hormone, insulin-like growth factor-1, and insulin-like growth factor-binding protein-3, but it does not affect the levels of other hormones. It is recommended as appetite stimulant for patients with cancer-induced cachexia.

Megestrol is a synthetic human hormone progesterone. Its anti-tumor effect on breast cancer, as well as the mechanism of action in anorexia and cachexia remains unknown. Administration of megestrol brings about weight gain caused by appetite stimulation. One cannot rule out a potential inhibitory effect of megestrolon the synthesis of interleukins associated with cachexia. Megestrol is indicated for treatment of anorexia and weight loss in patients with malignant tumors and acquired immune deficiency syndrome.

Synthetic analogs of tetrahydrocannabinol are used to manage nausea and stimulate appetite in patients undergoing chemotherapy (fig. 10.3). Cannabinoids for oral administration have a central sympathomimetic effect; they exert an effect on specific cannabinoid receptors in the central nervous system.

Dronabinol℘[2] is a trans-isomer of tetrahydrocannabinol; this is a non-selective agonist of cannabinoid receptors type 1 and type 2. The drug is approved for use in a limited number of countries. It effectively prevents side effects in oncologic patients receiving chemotherapy (antiemetic effect) and helps to manage weight loss syndrome in patients with AIDS-associated cachexia.

Some psychotropic substances (chlorpromazine amitriptyline, lithium carbonate) and anabolic steroids also exhibitan appetite stimulating effect.

Appetite Suppressants (Anorectics)

Anorectic drugs are used to treat obesity caused by excessive food consumption. Treatments for obesity include exercise, dietary therapy, pharmaceutical therapy, and surgery in case of morbid obesity (fig. 10.2).

Approaches to Diet-Induced Obesity Management

The most efficient approach to treating diet-induced obesity is the dietary approach, but patients with excess weight cannot follow a diet for a long period of time due to increased appetite and impaired mechanisms of satiety. In such cases, the patients receive anorectics (fig. 10.3).

Liraglutide is an analog of glucagon-like peptide-1; its amino acid sequence corresponds to endogenous peptide-1 by 97%. It has high affinity for glucagon-like peptide-1 receptor. Glucagon-like peptide-1 appears to be a physiologic regulator of appetite. Liraglutide promotes weight loss by reducing visceral fat rather than subcutaneous fat. It acts as a regulator of appetite increasing the feeling of full stomach and satiety and reducing hunger and food intake expectation, thus leading to areduction in food consumption. Liraglutide does not increase energy consumption as compared with placebo. Liraglutide is indicated in addition to dietary therapy and increased exercise to treat patients who have a body mass index >30 kg/m^2.

Lorcaserin℘ is a highly selective 5-HT$_2$C serotonin receptor agonist. It activates arcuate nucleus neurons of the hypothalamus leadingto excretion of α melanocortin stimulating hormone that excites melanocortin type 4 receptors in the paraventricular nucleus inhibiting appetite. It is used in addition to dietary therapy and increased exercise in patients with body mass index >30 kg/m^2 or 27 kg/m^2, arterial hypertension, diabetes mellitus type 2, or dyslipidemia.

Sibutramine and its two active metabolites stimulate noradrenergic and serotonergic synaptic junctions in the central nervous system (inhibiting neuronal reuptake of noradrenalin and serotonin, while having no effect on noradrenalin and serotonin secretion), thus inhibiting the hunger center and stimulating the satiety center.

Sibutramine reduces appetite and food intake (increasing the feeling of satiety), increases thermogenesis (as a result of indirect activation of beta-2 adrenergic receptors), and exerts an effect on brown adipose tissue. In *in vitro* studies, active metabolites of sibutramine also inhibit reuptake of dopamine, but they do it 3 times less actively than they inhibit reuptake of 5 HT and noradrenalin. Sibutraminehas a positive effect on lipid metabolism: it increases the concentration of HDL and reduces the levels of triglycerides, total cholesterol, LDL, and uric acid. Indications for use: overall supporting therapy of patients with excess weight in diet-induced obesity who have body mass index ≥30 kg/m^2 or over 27 kg/m^2, if patients have other risk factors caused by excess weight (diabetes mellitus type 2, or dyslipoproteinemia).

Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor group. Fluoxetine has a moderate anorectic effect associated with inhibition of neuronal reuptake of serotonin in the satiety center. Moreover, fluoxetine has a stimulant effect: it enhances mood, reduces stress, and reduces sensation of fear and dysphoria. Fluoxetine helps to increase serotonin concentration in cerebral structures, thus extending the duration of stimulating effect of serotonin on the nervous system. Bulimia nervosa is an indication for administration of fluoxetine (in addition to psychotherapy in order to reduce uncontrolled consumption of food).

10.2. ANTIEMETIC DRUGS

Vomiting is a normal, protective mechanism to eliminate toxic substances that have been ingested. This process involves peripheral and central mechanisms. The central part of the reflex includes the chemoreceptor trigger zone (CTZ) within the *area postrema* and the vo-

[2] Manufacturing, sale, import, and storage of tetrahydrocannabinol (including its synthetic pharmaceutical forms) are prohibited under the legislation of the Russian Federation, whereas the substance has been added to the List of Narcotic Substances, Psychotropic Substances, and Their Precursors, subject to control in the Russian Federation.

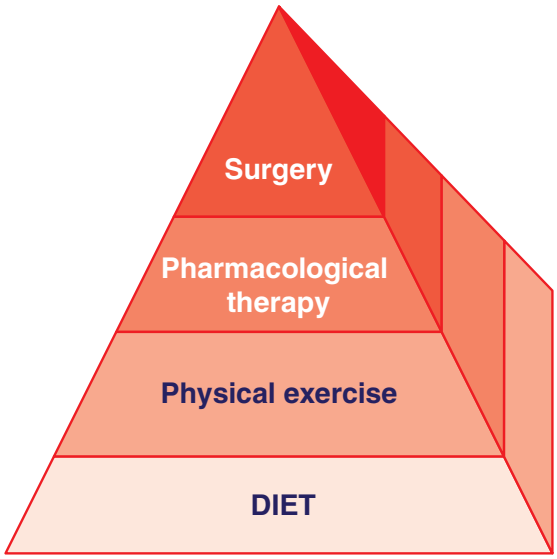

Fig. 10.2. Key principles of obesity management

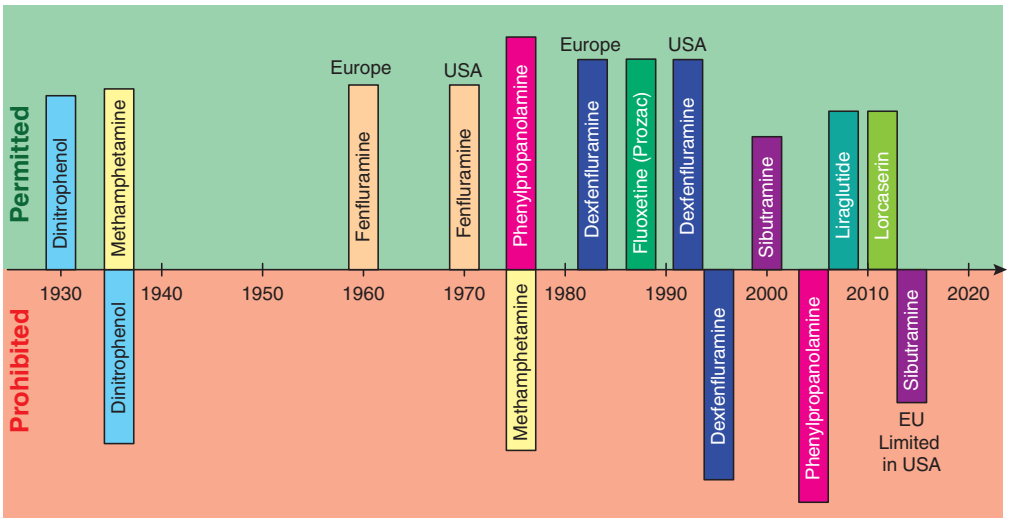

Fig. 10.3. History of appetite suppressants

miting center located in the medulla oblongata (fig. 10.4).

Excessive vomiting may become a pathologic condition leading to loss of fluid and electrolytes.

Vomiting may be caused by the following conditions:

- sea sickness;
- viral and bacterial infection;
- food intolerance;
- surgery;
- pregnancy;
- pain;
- shock;
- effect of certain medications;
- exposure to radiation;
- middle ear disease affecting the equilibrium.

Vomiting occurs after stimulation of either the CTZ or the vomiting center. The neurons of these centers contain receptors sensitive to

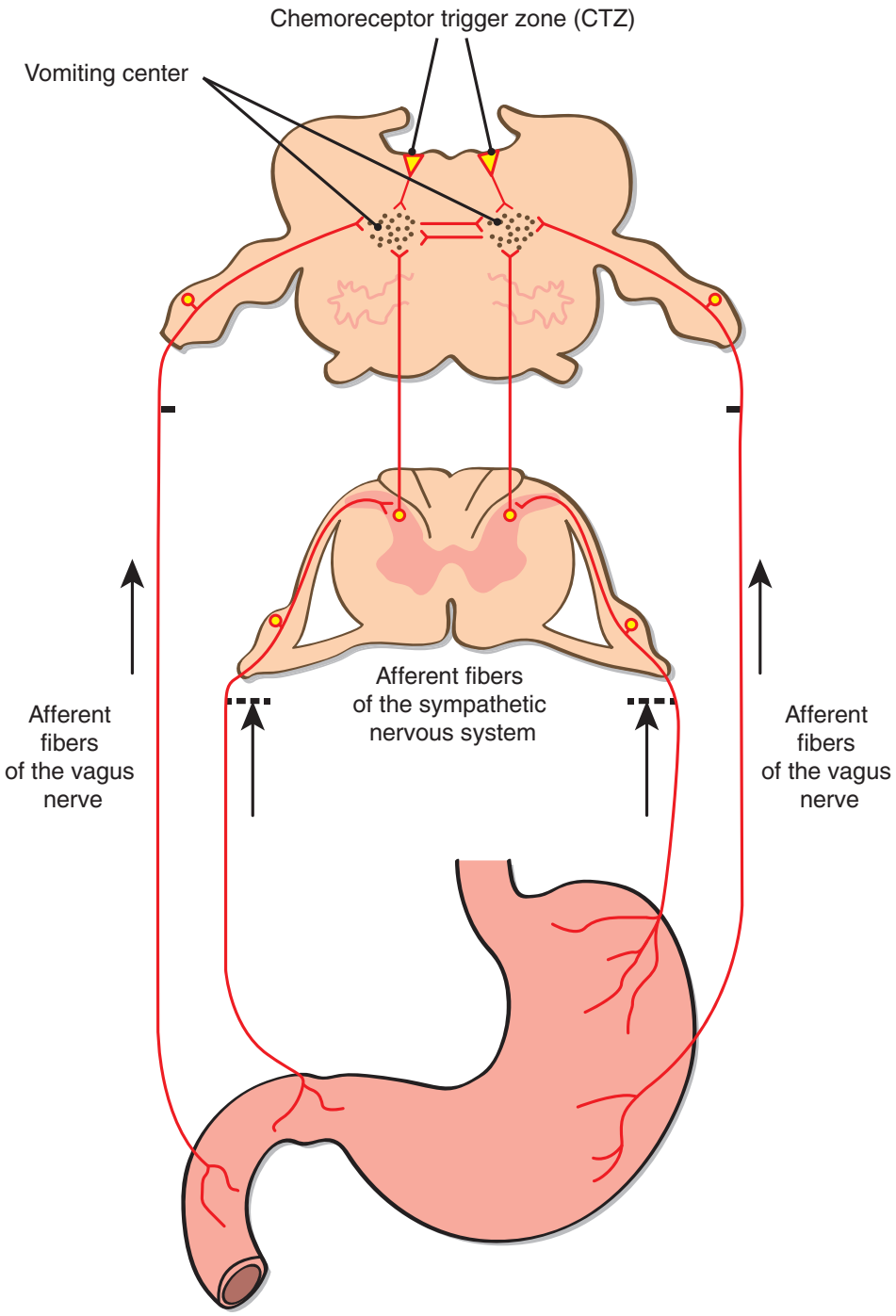

Fig. 10.4. Neuronal connections of the vomiting center. The vomiting center contains sensation, motion, and control nuclei mostly within the medulla oblongata and reticular formation of the pons

certain mediators of the central nervous system (fig. 10.5). The CTZ can be stimulated by narcotic analgesics, toxins, and through excitation of the inner ear vestibular system. These impulses are transferred to the vomiting center by the mediator dopamine. Acetylcholine and sensory impulses, such as smell and taste, are vomiting stimulants. Irritation of the stomach mucosa is transmitted directly to the vomiting center. Stimulation ofthe vomiting centerleads to activation of the motor neurons, which results in contraction of the diaphragm and muscles of the anterior abdominal wall and stomach. The epiglottis closes, the abdominal wall moves upward, and the contents of the stomach flow back into the esophagus.

Antiemetic drugs exert their effects by blocking the receptors of the central nervous system, CTZ, and vomiting center (see fig. 10.5).

- **Muscarinic receptor antagonists.**
  - **Scopolamine** and atropine have similar effects on the peripheral cholinoreactive systems; scopolamine induces all specific cholinoblocking effects: pupil dilatation, accommodation paralysis, heart rate acceleration, smooth muscle relaxation, and reduced secretion, including reduced gastrointestinal tract secretion. Unlike atropine, scopolamine suppresses the central nervous system, thus causing a sedative and, sometimes, soporific effect, reduced motor activity and respiratory suppression. Scopolamine suppresses transmission of impulses from descending pyramidal tracts to motor structures of the spinal cord, and blocks cholinoreactive structures of the reticular formation. As an antiemetic and sedative agent, it is included in the composition of Aeron℘, a medicine for motion sickness (often referred to as sea sickness) and air sickness.
- **H_1-antagonists:** promethazine, doxylamine, cyclizine℘, meclozine (meclizine).
  - **Promethazine** is a histamine H_1-receptor antagonist; it has a pronounced antihistamine effect and significant inhibiting influence on the central nervous system. It exerts sedative and antiemetic effects. It also has significant adrenoblocking and moderate peripheral and central cholinoblocking activity.
  - **Doxylamine** blocks histamine H_1-receptors, exerts an M-cholinoblocking effect. It reduces the time needed to fall asleep, enhances the duration and quality of sleep, and does not affect sleep phases.
- **Serotonin ($5\text{-}HT_3$) receptor antagonists:** granisetron, ondansetron, dolasetron℘, palonosetron.
  - **Granisetron** is an antiemetic agent that selectively bocks serotonin 5-HT3 recep-

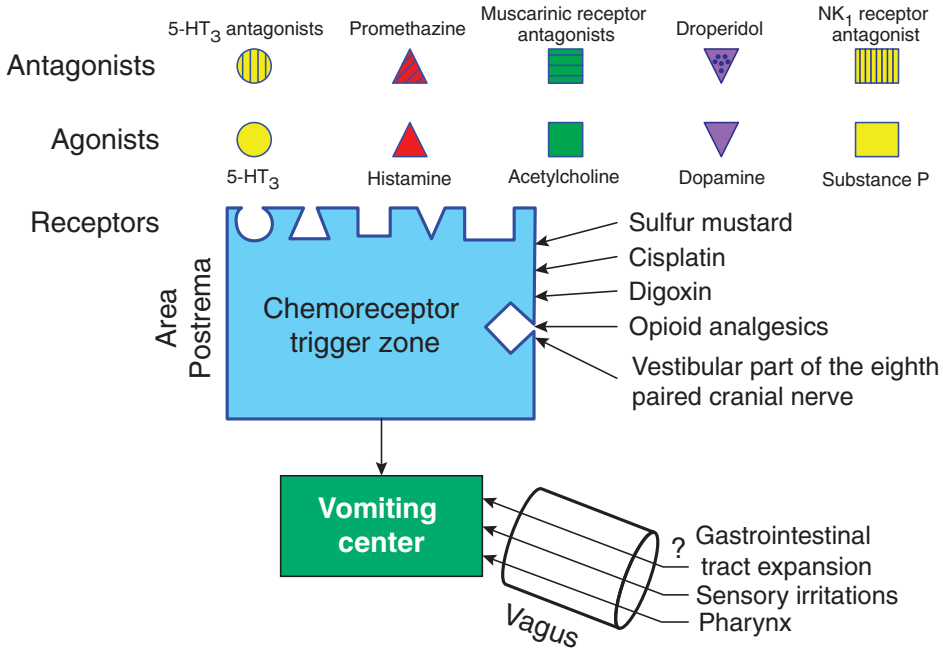

Fig. 10.5. Pharmacological regulation of the vomiting center activity

tors located at the terminals of the vagus nerve and in the trigger zone of the floor of the fourth ventricle of the brain and solitarii of the vomiting center of the brain stem. It does not interact with other serotonin and dopamine receptors. Side effects include stomachache, constipation or diarrhea, flatulence, headache, insomnia, sleepiness, unduetiredness or weakness, arrhythmia, chest pain, arterial hypotension or hypertension, skin rash, hyperthermia, and bronchial spasm.

- **Dopamine antagonists: haloperidol, chlorpromazine,** olanzapine, domperidone, metoclopramide, levosulpiride℘.
  - — **Haloperidol** blocks postsynaptic dopamine receptors located in the trigger zone of the vomiting center (antiemetic effect), extrapyramidal system, mesolimbic system (antipsychotic effect), and hypothalamus (hypothermia and galactorrhea); it blocks alpha-adrenergic and muscarinic acetylcholine receptors. A powerful antiemetic effect is combined with sedation. Side effects include anxiety, excitement, fear, akathisia (inability to stay still), movement dystonia, arterial hypotension, postural hypotension, decreased appetite, dry mouth, hyposalivation, and constipation.
  - — **Domperidone** is a dopamine D_2-receptor antagonist with anantiemetic effect due to a combination of peripheral (gastrokinetic) action and blocking chemoreceptor of the trigger zone of the vomiting center. It does not pass through the blood-brain barrier easily; however, in the CTZ area, the blood-brain barrier is not well developed. Domperidone extends the duration of peristaltic contractions in the pyloric antrum and duodenum accelerating its emptying if this process slows down, and increases the tone the lower esophageal sphincter. Domperidone increases plasma prolactin levels. Side effects include spasm of smooth muscles of the gastrointestinal tract, dry mouth, constipation/diarrhea, extrapyramidal symptoms, headache, asthenia, nervousness, increased plasma prolactin levels, galactorrhea, and gynecomastia.
  - — **Metoclopramide** is a D_2-dopamine receptor antagonist; it reduces the activity of the trigger zone of the vomiting center. Like domperidone, it has a prokinetic effect by stimulating enteric 5-HT_3-receptors.
- **Itopride** activates gastrointestinal peristalsis through a block of D_2-dopamine receptors and stimulation of cholinergic innervation induced by the drug's anti-cholinesterase activity. Itopride prevents the breakdown of acetylcholine by the enzyme and increases acetylcholine secretion from presynaptic terminals. Through interaction with CTZ dopamine receptors, it has an antiemetic effect and accelerates evacuation of the stomach contents. It does not alter plasma heparin concentration. It is indicated for treatment of functional non-ulcer dyspepsia, i.e. in case of sensation of overfilled stomach, epigastric discomfort, anorexia, heartburn, nausea, and vomiting.
  - — **Levosulpiride**℘ is the levorotatory enantiomer of sulpiride; it exerts its antiemetic and prokinetic effect by blocking CTZ dopamine receptors and activating 5-HT4 serotonin receptors.
- **NK_1 receptor antagonists** impede CTZ stimulation by substance P which has an emetic action at the following three levels of the central nervous system: nucleus of the vagus nerve, nucleus of the solitary tract, and in the *area postrema*. NK1 receptor antagonists are effective antiemetic drugs to be used during chemotherapy and in postoperative period. As of today, **aprepitant, rolapitant**℘, and netupitant℘ are used for this purpose. The most common side effects include dyspeptic disorders, weakness, sleepiness, and increased activity of hepatic transaminase.
- **Cannabinoids** (dronabinol℘, nabilone℘) have an antiemetic effect during chemotherapy of malignant tumors. The mechanism of their action remains unknown.

The efficacy of drugs used to treat vomiting depends on the underlying cause:

1) movement sickness, sea sickness, vestibular disorders (for instance, Ménière's disease):
   - — muscarinic receptor antagonists, *scopolamine*;
   - — H_1-antagonists: *promethazine, doxylamine, cyclizine*℘*, meclozine*;
2) gastroenteritis:
   - — *bismuth preparations*;
3) chemotherapy:
   - — serotonin (5-HT_3) receptor antagonists: *dolasetron*℘*, granisetron, ondansetron, palonosetron*;
   - — dopamine antagonists: *chlorpromazine, haloperidol, olanzapine, domperidone, metoclopramide, levosulpiride*℘;
   - — NK_1-receptor antagonists: *aprepitant, rolapitant*℘;
   - — glucocorticoids: *dexamethasone*;
   - — cannabinoids: *dronabinol*℘*, nabilone*℘;

4) surgery:
   — serotonin (5-HT_3) receptor antagonists: *dolasetron℘, granisetron, ondansetron, palonosetron*;
   — dopamine antagonists: chlorpromazine, haloperidol, *olanzapine, domperidone, metoclopramide, levosulpiride℘*;
   — NK_1-receptor antagonists: *aprepitant, rolapitant℘*;
   — glucocorticoids: *dexamethasone*;
5) vomiting of pregnancy:
   — vitamin B_6 (*pyridoxine*);
   — antihistamines: *doxylamine, promethazine*;
   — if there is no effect, *metoclopramide* is indicated.

10.3. DRUGS USED IN THE TREATMENT OF PEPTIC ULCER

Gastric ulcer is a local mucosal defect (sometimes with involvement of submucous membrane) which appears under the influence of hydrochloric acid, pepsin, and bile and causes trophic disturbances in that area.

Secretion of hydrochloric acid in the stomach is a complex process regulated either by the central nervous system or by humoral mechanisms. The neuronal (acetylcholine), paracrine (histamine), and humoral (gastrin) systems regulate the secretion of hydrogen ions in the gastric lumen by parietal cells. In addition, secretion of hydrochloric acid is regulated by the cholinergic system of enterochromaffin cells of the stomach. Acetylcholine secreted by fibers of this system stimulates M_1 receptors of enterochromaffin cells, thus enhancing histamine secretion.

On the basolateral membranes of parietal cells, there are muscarinic M_3 receptors, H_2 histamine receptors, and CCK2 receptors which ensure stimulation of hydrogen ion secretion. H_2 receptors are coupled to G_S protein. Excitation of these receptors (by means of cyclic adenosine monophosphate protein kinase dependent mechanisms) leads to activation of H^+/K^+-dependent adenosine triphosphatase ("proton pump"). This enzyme ensures replacement of protons from cytoplasm with potassium ions through the parietal cell membrane. In this case, pH gradient ranges from 7.8 inside the cell to 0.8 outside the cell (fig. 10.6).

The gastric mucosa has its own protective mechanisms against the acidic environment, which include the following:

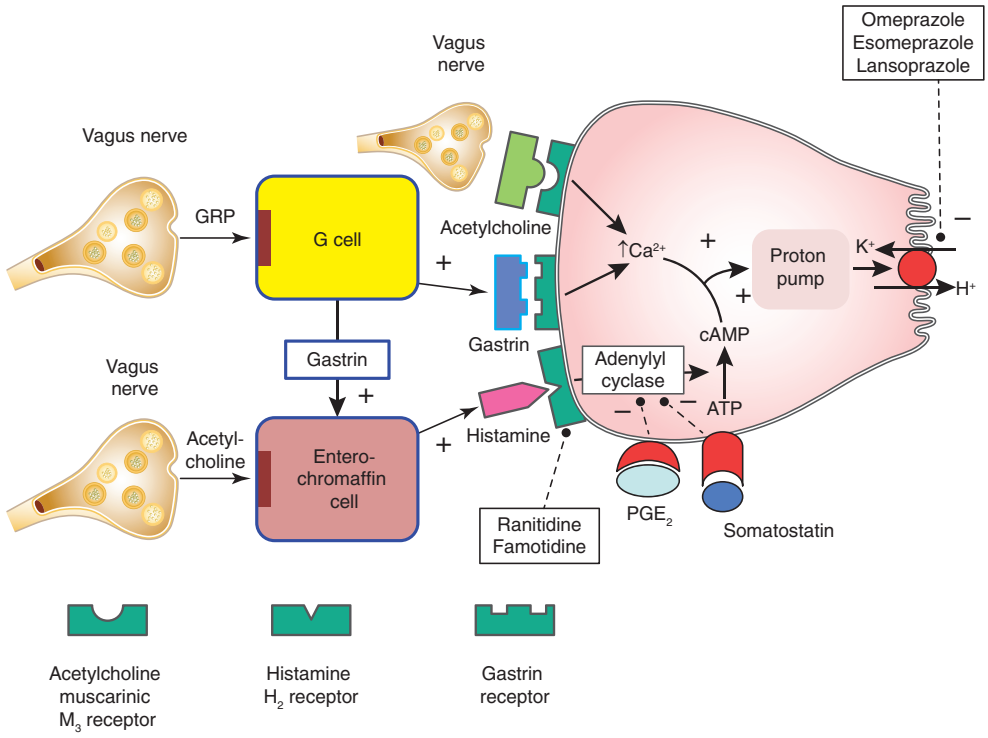

Fig. 10.6. Pharmacological regulation of hydrochloric acid secretion

- mucus production (hydrophilic lipoproteins) forming a system that protects the stomach epithelium against enzymes and acid. Mucus production requires intense blood supply and is regulated by prostaglandins E_2 and I_2, which, in addition to this, inhibit the secretion of hydrochloric acid (see fig. 10.6);
- intense blood supply ensures removal of hydrochloric acid penetrating through mucus;
- production of hydrogen carbonates by the superficial gastric mucous cells;
- internal protective mechanisms of the stomach epithelial cells.

Intensive secretion of hydrochloric acid and an imbalance between secretion and protective properties of the mucous membrane lead to development of gastroesophageal reflux disease and gastric ulcer.

The protective properties of the mucous membrane reduce *Helicobacter pylori* (HP) ingress. This bacterium is fixed by adhesion molecules to the gastric epithelial cells. In the duodenum, HP is fixed after metaplasia in the epithelium. Acid resistance of the bacterium is due to its capacity to produce urea which neutralizes hydrochloric acid around the bacterium. However, the resulting ammonia damages the stomach epithelium. Urease, lipase, and proteases secreted by HP contribute to damaging the mucous membrane (fig. 10.7).

It is important to remember that 5% of gastric ulcers become malignant.

Risk factors which may lead to gastric ulcers include the following.

- Medications:
  - non-selective non-steroidal anti-inflammatory drugs (including acetylsalicylic acid) with a local irritating effect on the gastric mucosa and inhibiting the synthesis of prostaglandins;
  - clopidogrel;
  - bisphosphonates;
  - nitrates;
  - potassium chloride;
  - corticosteroids;
  - antidepressants which represent selective inhibitors of serotonin reabsorption;
  - glucocorticoids in combination with non-steroidal anti-inflammatory drugs increase the risk of gastric ulcer.
- Lifestyle:
- alcohol: it damages the gastric mucosa;
- smoking: the risk is in direct proportion to the number of cigarettes smoked;
- tea, coffee, cola-containing beverages, milk, beer, and spicy food cause dyspeptic disorders without increasing the risk of gastric ulcer;
- stress.

Treatment objectives are as follows:

- eliminating signs of the disease;
- stimulating healing of gastric ulcer;
- preventing recurrence of gastric ulcers;

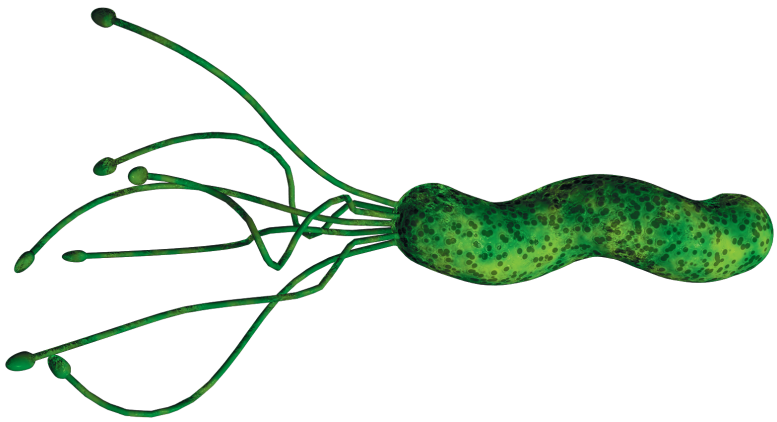

Fig. 10.7. *Helicobacter pylori* is a helix-shaped Gram-negative bacterium about 3 μm long with a diameter of about 0.5μm. It has 4 – 6 flagella and, due to flagella, it is highly motile even in dense mucus or agar. *H. pylori* is microaerophilic, i.e. it requires oxygen for its development but in the amount, which is much less than contained in the atmospheric air. Lipopolysaccharides and proteins in the outer wall of the bacterium demonstrate adhesion to the outer wall of the gastric mucosa cell membranes. Moreover, lipopolysaccharides of the outer wall of *H. pylori* cause the immune response of the host organism and development of the mucous membrane inflammation. Enzymes secreted by H. pylori cause the depolymerization and dissolution of protective mucus and damage to the gastric mucosa layer

- reducing the risk of complications;
- patients with a history of gastric ulcersshall undergo HP eradication therapy.

Treatment of gastric ulcers:

- if the patient is on non-steroidal anti-inflammatory drugs, they should be replaced with paracetamol or nonacetylated salicylates;
- lifestyle changes: avoiding consumption of food which can cause dyspeptic disorders;
- smoking shall be given up.

Pharmacological therapy

- Antacids: [magnesium oxide, magnesium carbonate, calcium carbonate, **aluminum hydroxide**℗, magnesium trisilicate, algeldrate + magnesium hydroxide (**Almagel**▲, **Maalox**▲), algeldrate + benzocaine + magnesium hydroxide (**Almagel A**▲), sodium bicarbonate] provide symptomatic treatment by neutralizing hydrochloric acid inthe stomach. Antacids can be used to treat symptoms of excess stomach acid and gastroesophageal reflux disease: heartburn, belching, periodic gastralgia, feeling of overfilled or heavy epigastric region, flatulence, dyspepsia, dyspepsia in pregnancy. Antacids containing bicarbonates and carbonates cause formation of carbon dioxide in the stomach. Liquid forms of medication are more effective than tablets. Antacids are not effective enough in case of severe secretion disturbances. These drugs are mainly used as symptomatic therapy. Antacids that contain aluminum may cause constipation and formation of insoluble phosphates in the intestinal tract, thus inhibiting absorption of insoluble phosphates from the gastrointestinal tract. Antacids that contain magnesium may cause diarrhea.
- Proton pump inhibitors (PPIs) (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole). Due to high effectiveness and more favorable benefit-risk ratio, these medications are considered the first-line drugs. PPIs are weak bases; in the acidic environment of the stomach they lose their ability to be absorbed (therefore, they are manufactured in acid resistant forms). The target of PPIs is H^+ and K^+-dependent adenosine triphosphatase of parietal cells of the gastric mucosa. PPIs are absorbed in the intestinal tract, then, being weak bases, they pass through the cell membrane into the parietal cells where, in the acidic environment of the canaliculi, they become active and irreversibly block H^+ and K^+-dependent adenosine triphosphatase. PPIs may bond to various parts of the proton pump; this depends on the mechanism of action of certain drugs.

Indications for short-term use of PPIs are benign gastric ulcer, gastroesophageal reflux disease, and ulceration of the gastric mucosa caused by non-steroidal anti-inflammatory drugs.

Indications for long-term use of PPIs include supporting therapy during treatment of Barrett's esophagus, hypersecretory conditions (Zollinger–Ellison syndrome), and complicated esophagitis.

Side effects of PPIs areheadache, nausea, vomiting, diarrhea, constipation, abdominal pain, and rash. PPIs intake during pregnancy and breastfeeding, or by patients with liver diseases, requires precautions. PPIs can mask symptoms of gastric cancer, thus, before any therapy with PPIs is started, malignant tumors of the stomach must be ruled out. PPIs increase the risk of diarrhea caused by *Clostridium difficile*.

It is important to remember that PPIs reduce conversion of clopidogrel (prodrug) to its active form due to inhibition of CYP450 2C19 microsomal enzyme of the liver; this can increase the risk of thrombus formation. Table 10.2 provides

Table 10.2. Influence of proton-pump inhibitors on metabolism of other drugs

Medication	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Carbamazepine	↓ Metabolism	Unknown	–	Unknown
Clarithromycin	–	–	Unknown	Unknown
Diazepam	↓ Metabolism	–	–	–
Digoxin	↑ Absorption	Unknown	↑ Absorption	↑ Absorption
Ketoconazole	↓ Absorption	↓ Absorption		↓ Absorption
Methotrexate	↓ Renal excretion	Unknown	Unknown	Unknown
Nifedipine	↑ Absorption	Unknown	↑ Absorption	Unknown
Oral contraceptives	–	–	–	Unknown
Diphenine	↓ Metabolism	–	–	–
Warfarin	↓ Metabolism	–	–	–
Theophylline	–	↑ Metabolism	–	–

information about the influence of PPIs on the metabolism of other drugs.

- H_2 antagonists (**ranitidine, cimetidine, nizatidine, famotidine**). These drugs inhibit the effect of histamine on parietal cells by inhibiting histamine H_2 receptors on the surface of parietal cells, and reduce the secretion of hydrochloric acid.

Indications for the use of H_2 antagonists are identical to the indications for administration of PPIs; however, due to lesser effectiveness they are regarded the second line medications and are resorted towhen PPIs cannot be administered.

Side effects of H_2 antagonists include tiredness, headache, dizziness, abdominal discomfort, hyperprolactinemia, impotence, gynecomastia, amenorrhea, and, in aged patients, mental confusion and hallucinations.

H_2 antagonists inhibit microsomal enzymes of the liver, thus altering the metabolism of some other drugs.

- In the acidic environment of the stomach gastroprotective drugs like sucralfate, a basic aluminum salt of sulfated disaccharide, interact with necrotized tissues of the ulcer surface and form a film protecting against the effect of hydrochloric acid and pepsin. It stimulates secretion of bicarbonates and slightly inhibits pepsin activity.

Indications for administration include acute peptic ulcers, esophagus ulceration.

Side effects of sucralfatearedry mouth, constipation, and rash.

In patients with renal failure, plasma aluminum levels shall be monitored.

Misoprostol is an analog of synthetic prostaglandin E1 that stimulates secretion of mucus, synthesis of bicarbonates, surfactant-like phospholipids, and increases blood flow in the gastric wall. It is used to prevent and treat peptic erosions and ulcers in patients receiving non-steroidal anti-inflammatory drugs and glucocorticoids.

Contraindication: pregnancy.

Side effects are headache, vomiting, and diarrhea.

- **Bismuth subcitrate potassium** is a gastroprotective and antiulcer drug which has an antibacterial effect on HP. In the acidic environment of the stomach, chelate compounds are formed with a protein substrate in the form of a protective film on the ulcer surface. Bismuth subcitrate potassium enhances the synthesis of prostaglandins.

Indications for use include duodenal ulcer, as well as HP-associated duodenal ulcer, chronic gastritis, and irritable bowel syndrome.

Side effects are black stool, nausea and vomiting in rare cases.

Contraindications: pregnancy and breastfeeding.

To manage HP infection, antibacterial medications are administered.

- Antibiotics (**clarithromycin, amoxicillin, tetracycline**).
- Synthetic antibacterial medications (**metronidazole**).

The properties of antibacterial drugs are discussed in Chapter 17. *Chemotherapeutic Agents. Antibiotics***.**

The algorithm for treating duodenal ulcerdiseaseincludes administration of medications that reduce the secretion of gastric glands and antibacterial therapy leading to eradication of HP, the so-called triple therapy, and, if it turns out to be ineffective, quadruple therapy (table 10.3).

1. Selection of *H. pylori* eradication tactics shall depend on the regional (populational) resistance of the microorganism to clarithromycin, metronidazole, and fluoroquinolones. Moreover, it is important to consider the personal history of taking antibacterial drugs.

2. Standard therapy is not recommended in a population with high prevalence of *H. pylori* clarithromycin resistance. The threshold of high resistance of microorganism to antibiotics is 15%. In this case, eradication therapy shall be started with quadruple therapy (containing bismuth), or with non-bismuth quadruple therapy that does not contain clarithromycin. The levofloxacin-based protocol is used when the first-line therapy is ineffective.

3. Standard triple and bismuth-containing quadruple therapy should be administered for a period of 14 days. It is recommended to extend the duration of sequential and accompanying therapy for up to 14 days.

4. Almost all new versions of eradication protocols imply administration of double dose of PPIs two times a day; most often, esomeprazole is administered in the amount of 40 mg 2 times a day.

5. Most statements of the Maastricht V/Florence Consensus Report on *H. pylori* eradication treatment have a low or a very low level of evidence and a weak grade of recommendations.

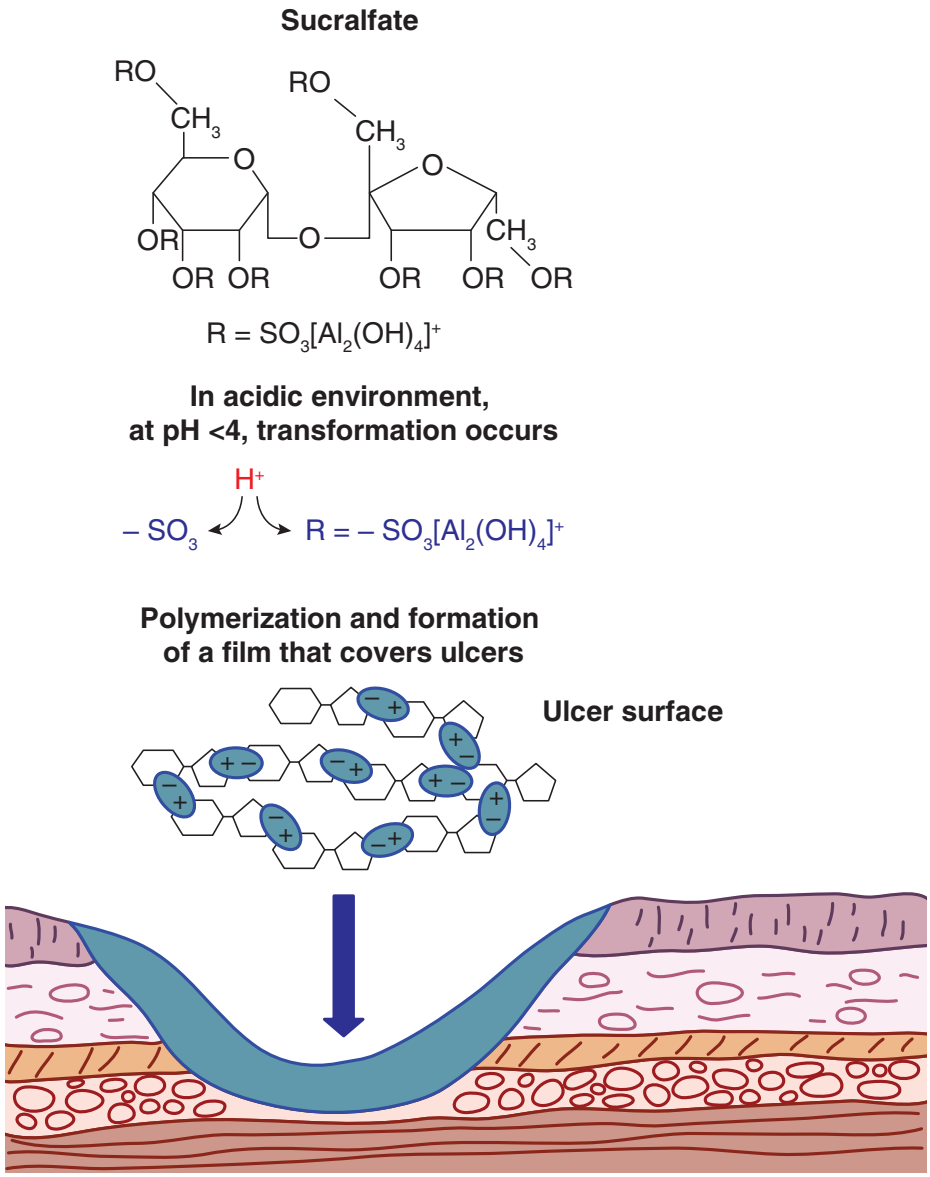

Fig. 10.8. Mechanism of action of sucralfate

6. A large-scale clinical trial, called the CLARICOR trial, reported an increased risk of death among patients with coronary heart disease who received a two-week course of clarithromycin. Macrolides block specific cardiac potassium channels (IKr) encoded by the hERG (human ether-a-go-go-related gene), which increases the risk of ventricular tachyarrhythmia in patients with primary long QT interval syndrome. Moreover, QT prolongation is associated with hypokalemia, hypomagnesemia, and with administration of class IA and III antiarrhythmic drugs. In all these situations, concomitant administration of clarithromycin may lead to an increased risk of serious arrhythmia.

Table 10.3. Peptic ulcer management regimen

Drug No.1	Drug No.2	Drug No.3	Drug No.4	Course duration
PPI-containing triple therapys				
PPI 2 times a day	Clarithromycin 0.5 2 times a day	Amoxicillin 0.1 2 times a day		7 days
Bismuth-containing quadruple therapy				
PPI or H_2 antagonist 2 times a day	Bismuth subcitrate potassium 0.525 4 times a day	Metronidazole 0.5 3 times a day	Tetracycline 0.5 4 times a day	10 days
Sequential therapy				
PPI 1–2 times a day (10 days)	Amoxicillin 1.0 2 times a day (days 1–5)	Metronidazole 0.25–0.5 2 times a day (days 6–10)	Clarithromycin 0.5 2 times a day (days 6–10)	10 days
Second-line therapy for persistent infection				
PPI or H_2 antagonist 2 times a day	Bismuth subcitrate potassium 0.525 4 times a day	Metronidazole 0.25–0.5 4 times a day	Tetracycline 0.5 4 times a day	
PPI 2 times a day	Amoxicillin 1.0 2 times a day	Levofloxacin 0.5 2 times a day	Tetracycline 0.5 4 times a day	
PPI 2 times a day	Amoxicillin 1.0 2 times a day	Clarithromycin 0.5 2 times a day	Metronidazole 0.5 4 times a day	

10.4. DRUGS AFFECTING GASTROINTESTINAL MOTILITY AND SECRETION

Laxatives

Constipation means very rare, hard, or systematically insufficient defecation (intestinal discharge). Among Europeans the frequency of defecation ranges from 2 times a week to 3 times a day.

Gastrointestinal tract peristalsis is controlled by the vegetative nervous system, a special dedicated part thereof, the enteric nervous system, as well as by various hormones. The enteric nervous system is embedded in the lining of the gastrointestinal wall and is represented by two connected networks: myenteric (Auerbach's) plexus, located between the longitudinal and circular layers of the muscular layer, and submucosal (Meissner's) plexus. Stimulation of mucosal mechanoreceptors and chemoreceptors provokes release of serotonin from enterochromaffin cells, which excite primary afferent neurons (1) bound to ascending (2) or descending (3) internuncial neurons of the local reflex pathways. The reflex causes contraction of the parietal intestine in response to activation of motor neurons (6) and relaxation of the distal part by inhibitory neurons (5), thus providing peristalsis (fig. 10.9).

Constipation causes include

Imbalanced diet:
- insufficient consumption of vegetable fibers;
- insufficient water intake.

Insufficient physical activity.

Diseases:
- anal fissure;
- irritable bowel syndrome;
- Hirschsprung's disease;
- rectal prolapse;
- diverticular disease of the large intestine;
- amyloidosis;
- porphyria;
- hypothyroidism;
- Parkinson's disease;
- endometriosis.

Medications:
- muscarinic receptor antagonists (atropine and atropine-like medications, typical neuroleptics, tricyclic antidepressants);
- antacids containing aluminum and calcium;
- iron sulfate
- barium preparations, bismuth preparations;
- narcotic analgesics;
- antidepressants;
- antiparkinsonian medications;
- calcium channel blockers.

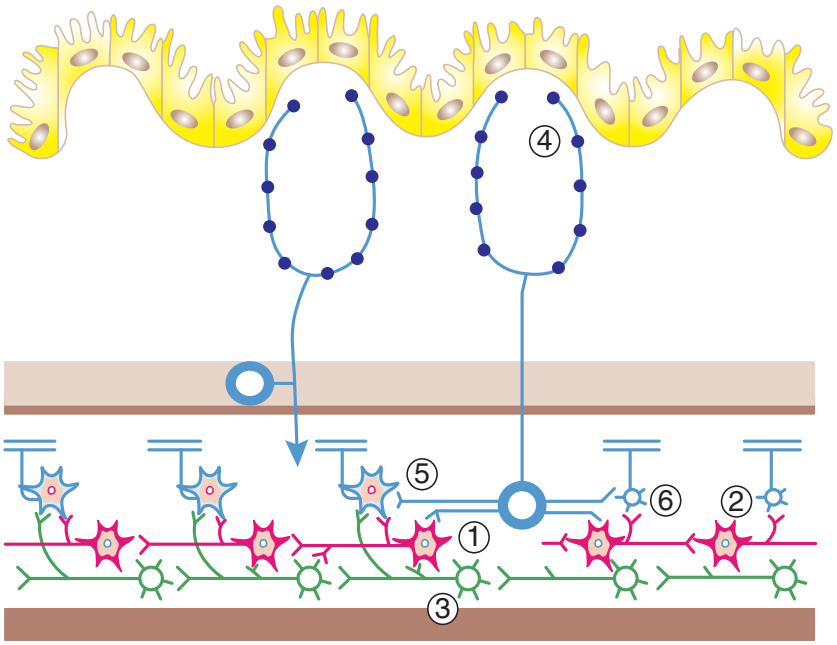

Fig. 10.9. Neural network that regulates peristalsis: 1 — primary afferent neurons, 2 — bound neurons, 3 — descending neurons, 4 — afferent terminals, 5 — inhibitory neurons, 6 – motor neurons

Laxatives

If increased physical activity, increased water intake and vegetable fibers consumption produce no effect, it is necessary to administer laxatives to facilitate defecation (fig. 10.10).

The following groups of laxatives are distinguished.

- **Laxatives that increase intestinal contents.** These contain hydrophilic colloids from indigestible parts of plants **(agar-agar, laminaria, bran, methylcellulose, carboxymethylcellulose)**. Colloid formation increases the volume of intestinal contents, thus promoting perstalsis by stimulating mechanoreceptors in the colon wall. Disadvantages of this group of laxatives include a long latent period (1–3 days) and disturbance of absorption, including absorption of some medications (cardiac glycosides).
- **Stimulant laxatives**. These laxatives are metabolized into active compounds, which stimulate chemoreceptors of the intestinal wall and enhance peristalsis.
  - — **Bisacodyl** is a prodrug that is not absorbed from the intestinal tract; it is activated in the alkaline environment of the colon and stimulates chemoreceptors, thus exerting a laxative effect. After oral administration, the onset of action iswithin 5–7 hours; after rectal administration in the form of a suppository, the onset of action is within 1 hour.
  - — Anthraquinone glycosides, which are active ingredientsof **senna, rhubarb, and buckthorn** preparations, are absorbed in the small intestine and released in the colon, where they directly stimulate local chemoreceptors, thus stimulating secretion of electrolytes and water; anthracene derivatives enhance peristalsis. The laxative effect starts in 8–12 hours.
  - — **Sodium picosulfate** is not absorbed in the small intestine; in the colon it is metabolized bycolonic bacterial flora to free diphenol. This compound stimulates chemoreceptors of the colon producing a laxative effect which manifests in 8–12 hours.
  - — **Castor oil** (vegetable oil pressed from castor beans): after oral administration ricinoleic acid is released by lipase in the duodenum. This substance stimulates intestinal receptors, inhibits ion transport and water absorption. This leads to enhanced motility of the intestinal tract throughout its entire length and accelerates defecation. The laxative effect starts in 2–6 hours. Castor oil is used in case of acute constipation. Castor oil is contraindicated in case of intoxication caused by fat-soluble compounds.

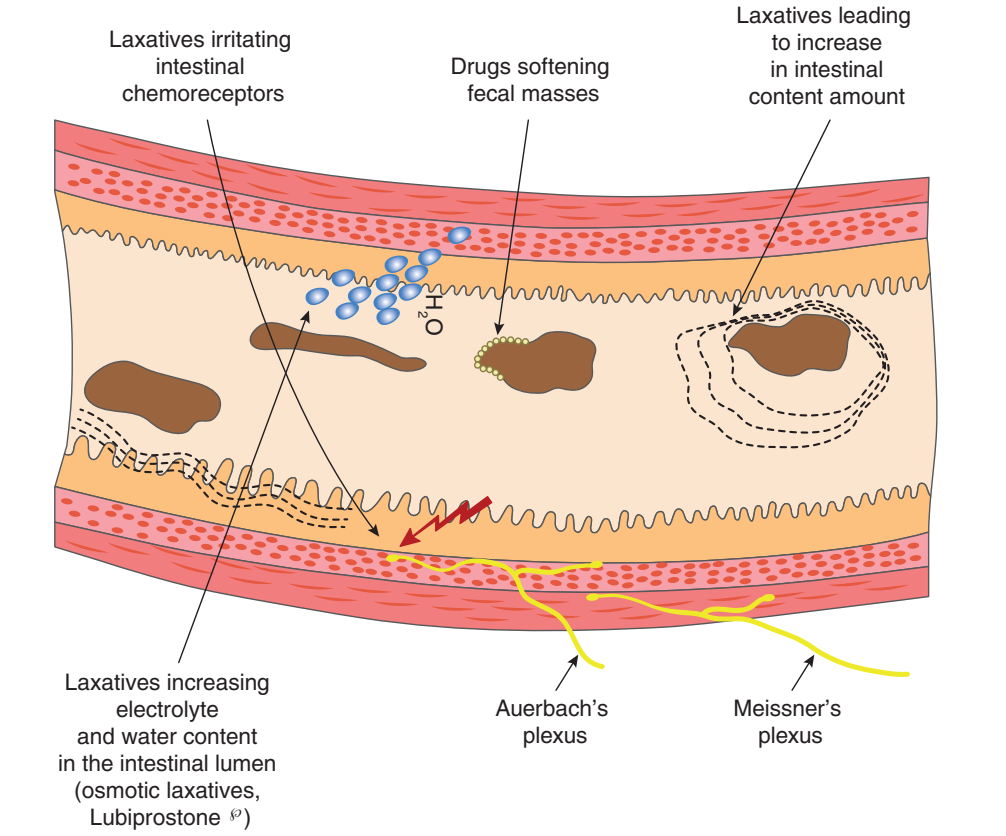

Fig. 10.10. Mechanism of action of laxatives

- **Osmotic laxatives** represent a group of different compounds poorly absorbed from the gastrointestinal tract; oral administration of such compounds causes slowdown of water absorption in the intestinal lumen as a result of elevated osmotic pressure.
  - **Sodium sulfate and magnesium sulfate** are used to treat cases of acute intoxication (to empty the intestinal tract and reduce absorption of toxic substances) and, less often, in case of acute constipation. They act throughout the entire intestinal tract; they are not used in treatment of chronic constipation as they inhibit absorption both in the small intestine and in the large intestine. They are administered in the dose of 15–20 g. Their side effects include nausea, vomiting, diarrhea, aggravation of gastrointestinal tract inflammatory diseases, electrolyte disorders (undue tiredness, weakness, mental confusion, arrhythmia, convulsions), tympanites, abdominal cramping, and abdominal pain.
  - **Lactulose** is a semi-synthetic disaccharide composed of fructose and galactose that cannot be hydrolyzed by any gastrointestinal enzyme. In the colon, bacterial enzymes hydrolyze lactulose into lactic, formic, and acetic acid. It elevates osmotic pressure, causing fluid accumulation which increases the volume of intestinal-contents, stimulates stretch receptors, softens the stool, thus facilitating defecation. Lactulose is used to treat chronic constipation.
- **Lubiprostone: a chloride channel activator. Lubiprostone** activates potential-dependent ClC-2 chloride channels on the apical surface of gastrointestinal epithelial cells. It results in increased secretion of electrolytes and fluid into the intestinal lumen, while the electrolyte composition of blood plasma remains unaltered. Lubiprostone does not have any systemic effect, as it is hardly absorbed from the gastrointestinal tract. Lubiprostone is used to treat chronic constipation. The course should not exceed 4 weeks. The drug is contraindicated for pregnant and breastfeeding patients.
- **Emollient and lubricant laxatives: liquid paraffin, almond oil.** These drugs remain unabsorbed after oral administration, they lubricate intestinal mucosa and soften the stool. A similar effect is exerted by **glycerin suppositories**. They are prescribed to manage chronic constipation.
- If the above-mentioned laxatives turn out to be ineffective, **prucalopride** is used as a 5-HT_4 receptor agonist, which, has a prokinetic effect due to its influence on the serotoninergic system of the intestinal tract.

The following drugs are used to treat irritable bowel syndrome accompanied by constipation:

Linaclotide is an intestinal guanylate cyclase 2_c receptor agonist. It acts as an analgesic in visceral pain, and stimulates intestinal cell secretion.

Trimebutine regulates the gastrointestinal function by acting on the intestinal enkephalinergic system. It binds to μ- and κ- opioid receptors, thus normalizing physiologic peristalsis of the gastrointestinal tract. The drug is used symptomatically for abdominal discomfort and cramps, abnormal frequency of bowel movements, and signs of irritable bowel syndrome.

The most common side effect of opioid administration in patients with cancer is constipation. **Methylnaltrexone** and **alvimopan** are opioid receptor antagonists used to manage opioid-induced constipation. These drugs do not pass through the blood-brain barrier and act by blocking peripheral opioid receptors. Thus, this drug eliminates only the peripheral effect of narcotic analgesics, not affecting their analgesic effect.

Antidiarrheal drugs

Diarrhea is acondition of having three or more liquid or loose stools in a day. However, in such a case, the stool consistency is more important than the number of defecations.

Non-infectious causes of diarrhea:

- medications (table 10.4):
  - **medications affecting gastrointestinal motility:** anticholinesterases, laxatives, macrolides, levothyroxine;
  - **medications increasing the intraluminal osmotic pressure:** Mg^+-containing antacids, acarbose, antibiotics;
  - **medications increasing the secretion or inhibiting reabsorption of ions:** non-steroidal anti-inflammatory drugs, quinidine, antineoplastic drugs, digoxin, misoprostol, omeprazole;
  - **medications inducing the intestinal wall inflammation:** non-steroidal anti-inflammatory drugs, simvastatin, antineoplastic drugs (including cytotoxic drugs), ranitidine, cyclosporine;
  - **inhibitors of carbohydrate and lipidabsorption:** acarbose, orlistat, colestipol, cholestyramine, metformin, tetracyclines.
- food allergy;
- gastrointestinal tract diseases (non-infectious enteritis and colitis);
- thyrotoxicosis;
- carcinoid syndrome.

Table 10.4. Mechanisms of drug-induced diarrhea development

Drug	Diarrhea development mechanism
Osmotic laxatives	Osmotic pressure increases in the intestinal lumen
Stimulating laxatives	Secretory diarrhea (excessive amount of liquid and salts)
Mg^{+}- containing antacids	Osmotic pressure increases in the intestinal lumen
Erythromycin	Diarrhea caused by hypermotility
Antibiotics	Pseudomembranous colitis
Non-steroidal anti-inflammatory drugs	Lymphocytic colitis and/or collagenous colitis
Alpha-glucosidase inhibitors	Carbohydrate absorption inhibition
Lipase inhibitors	Inhibition of fat absorption (steatorrhea)

Etiological agents of infectious diarrhea (table 10.5):

- bacteria: *Salmonella, Campylobacter, Shigella, E. coli 0157:H7, Clostridium difficile, Yersinia*;
- viruses: *Caliciviruses* (*Norovirus* and related viruses), *Rotavirus, Adenovirus* types 40 and 41, *Astrovirus*;
- protozoa: *Cryptosporidium*, *Giardia, Cyclospora, Entamoeba histolytica*;

Objectives of pharmacological therapy consist in:

- rehydration;
- symptomatic treatment;
- eliminating the cause of diarrhea.

Pharmacological Treatment of Diarrhea

Rehydration

Even in severe diarrhea, water and salts are still absorbed from the small intestine due to glucose-dependent active transport of sodium ions. Therefore, electrolyte administration is an efficient method to replenish liquid and water. Glucose is necessary to ensure active transport of sodium ions (table 10.6).

Table 10.6. Components of oral rehydration salts

Component	Concentration, mmol/liter
Sodium	75
Chloride	65
Anhydrous glucose	75
Potassium	20
Sodium citrate	10
Total osmolarity	245

Homemade Oral Rehydration Salts (ORS) Recipe:

- 1 teaspoon of salt;
- 8 teaspoons of sugar;
- 1 liter (five cups) of clean drinking water.

Symptomatic Therapy

The opioid system plays an important role in the regulation of the gastrointestinal tract motility and secretion. Opioid receptors are located on neurons embedded in the walls of the stomach and intestines and activated by endogenous opioids (enkephalins, endorphins,

Table 10.5. Etiological agents of diarrhea

Bacteria	Viruses	Protozoa	Helminths
Escherichia coli	*Rotavirus*	*Cryptosporidium parvum*	*Strongyloides stercoralis*
Campylobacter jejuni	*Norovirus*	*Giardia intestinalis*	*Angiostrongylus costaricensis*
Vibrio cholerae O1	*Adenovirus*	*Microsporida*	*Schistosoma mansoni*
Vibrio cholerae O139	*Astrovirus*	*Entamoeba histolytica*	*Schistosoma japonicum*
Shigella species	*Citomegalovirus*	*Isospora belli*	
Vibrio parahaemolyticus		*Cyclospora cayetanensis*	
Bacteroides fragilis		*Dientamoeba fragilis*	
Salmonellae		*Blastocystis hominis*	
Clostridium difficile			
Yersinia enterocolitica			
Yersinia pseudotuberculosis			

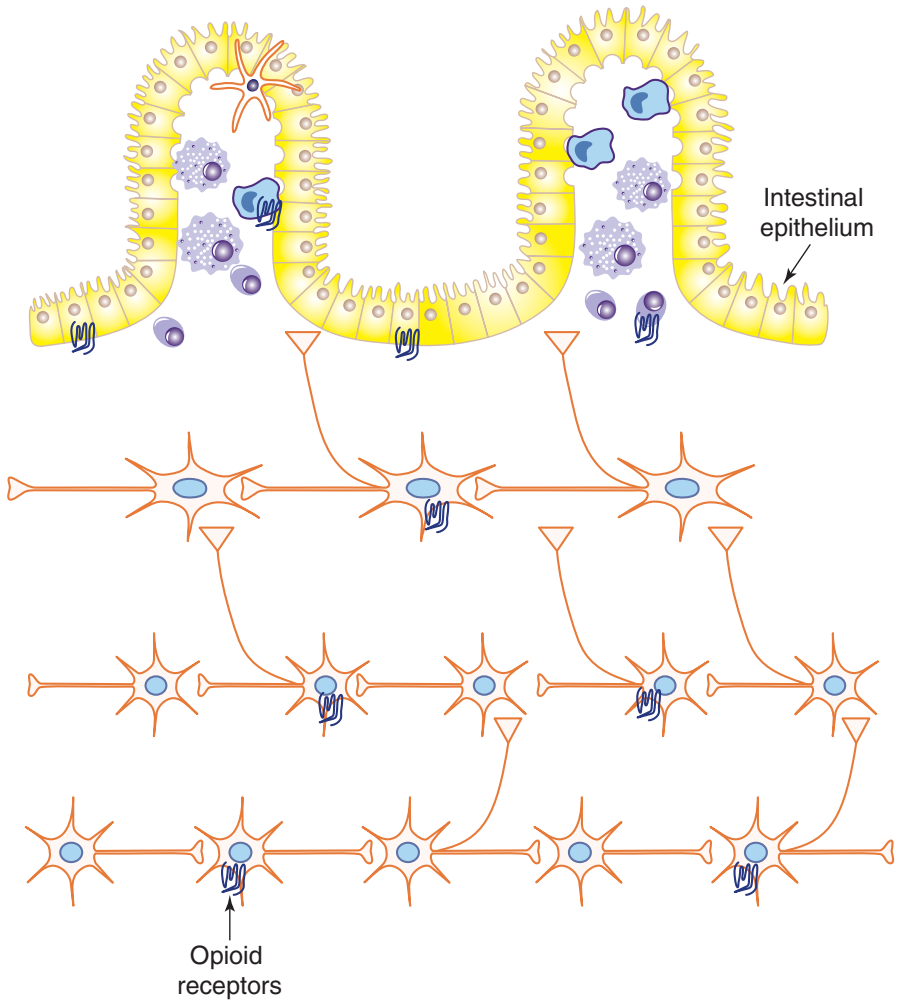

Fig. 10.11. Site of action of opioids in the gastrointestinal tract

dynorphins), as well as by exogenous opioids (loperamide, morphine), thus altering the gastrointestinal tract motility. Activation of μ-opioid receptors leads to inhibited activity of neurons of the excitatory and inhibitory pathways of the gastrointestinal motility regulation. Through inhibition of calcium channel conductance in presynaptic terminals μ-eceptor agonists, reduce the secretion of mediators (acetylcholine, serotonin) and inhibit postsynaptic neurons through activation of potassium channels, thus leading to hyperpolarization and slowing down cell activity. Inhibition of excitatory neurons leads to reduced peristalsis, and inhibition of inhibitory neurons increases the tone of sphincters.

Loperamide is a synthetic agonist of μ-opioid receptors. It inhibits peristalsis and secretion in the intestinal tract thus eliminating the signs of diarrhea. It increases the anal sphincter tone and reduces the urge to defecate. Loperamide does not penetrate the central nervous system, because it is a substrate for P-glycoprotein which prevents passing of lipophilic substances through cell membranes, including cerebral vascular endothelium.

Side effects of loperamide include sleepiness, dizziness, headache, dry mouth, stomachache, nausea, vomiting, constipation, abdominal discomfort and distension, pain in the upper parts of the abdomen, and rash. In rare cases, myosis and respiratory depression may occur as a result of loperamide penetrating the central nervous system. Loperamide should be avoided in patients with bloody diarrhea or with suspected inflammatory diarrhea (patients with fever) (fig. 10.9, 10.10).

Racecadotril is a prodrug that has an antisecretory effect; after oral administration, it is metabolized to thiorphan, which acts as an enkephalinase inhibitor by preventing breakdown of enkephalins in the intestinal wall. The drug causes an increase in endogenous opioid levels in the intestinal wall, thus leading to reduced secretion.

Eluxadoline℘ (not registered in the Russian Federation) is a new drug to treat diarrhea-predominant irritable bowel syndrome. Eluxadoline℘ is a μ-, κ-, and δ-opioid receptor antagonist. These properties allow reducing propulsive intestinal motility without increasing the sphincter tone (which can cause constipation). Eluxadoline℘ is hardly absorbed from the gastrointestinal tract, and the part of the drug that is absorbed into the bloodstream is metabolized during the first passage through the liver. Thereby, there is practically no risk of drug dependence. Post approval studies have shown that patients without a gallbladder who are receiving eluxadoline℘ therapy are at a significantly higher risk of developing severe pancreatitis leading to hospitalization or death. Pancreatitis may be caused by spasms of muscles in the small intestine.

Lactobacillus preparations help to inhibit the growth of pathogenic microorganisms and replace pathogenic microorganisms in the intestinal microflora. This leads to restoration of the intestinal function.

Bismuth subsalicylate, loperamide, as well as a combination of **diphenoxylate**℘**/atropine** may be used as alternative treatment in patients with diarrhea-predominant irritable bowel syndrome. Simethicone may also be administered.

Octreotide mimics endogenous somatostatin. It is used in symptomatic treatment of carcinoid tumors. It inhibits production of growth hormone and reduces the secretion of glucagon, insulin, serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. Reduced secretion of the specified biologically active compounds eliminates diarrhea.

It is important to remember that diarrhea may reduce the absorption of antiepileptic drugs, antimalarial medications, anti-HIV drugs, antidiabetic drugs, anticoagulants, and oral contraceptive pills.

The following medicines are usually administered to treat infectious diarrhea: antibiotics from among synthetic tetracyclines (doxycycline), macrolides (azithromycin), cephalosporins (ciprofloxacin, ceftriaxone), rifaximin (the form that is not absorbed from the gastrointestinal tract), chloramphenicol, as well as fluoroquinolones (norfloxacin), metronidazole, and tinidazole (table 10.7).

Table 10.7. Antimicrobial drugs to treat diarrhea

Microorganism	Drug	Dose, mg	Rate of administration per day
Cholera	Doxycycline	300	1
	Azithromycin	1000	1
	Ciprofloxacin	500	2
Shigellosis	Ciprofloxacin	500	2
	Ceftriaxone	2000–4000	1
	Pivmecillinam℘	400	3–4
Amoebiasis	Metronidazole	750	3
Giardiasis	Metronidazole	250	3
	Tinidazole	50 мг/кг	1
Campylobacter	Azithromycin	500	1
	Ciprofloxacin	500	1

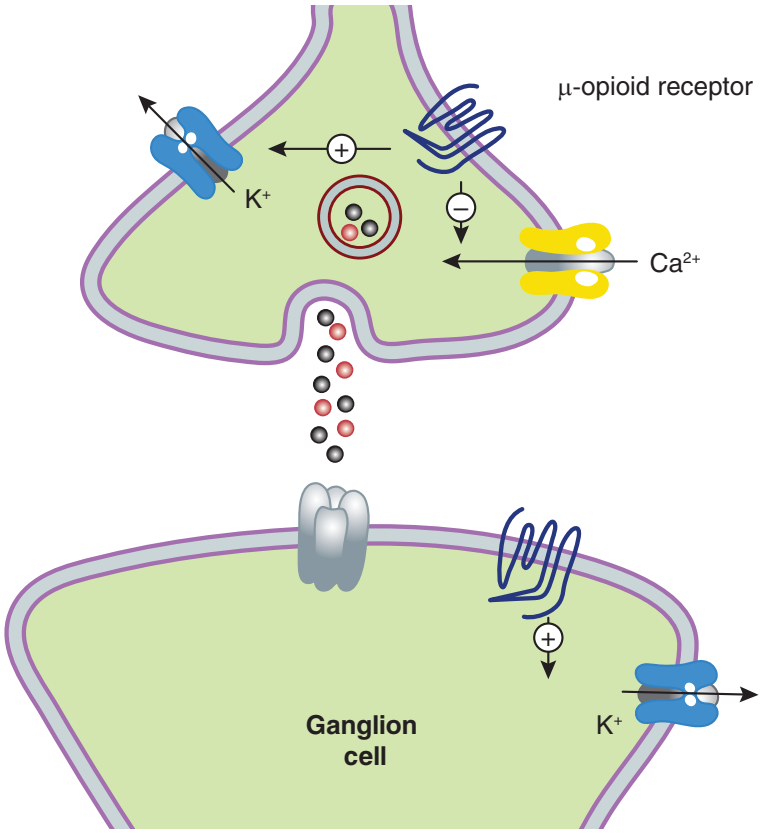

Fig. 10.12. The antidiarrheal effect of opioid receptor agonists is based on the following mechanisms: stimulationof μ-, κ- and δ - opioid receptors causes the inhibition of calcium channels. As a result, the mediator secretion from presynaptic terminals decreases and the excitability of postsynaptic neurons weakens. The stimulation of these receptors results in the activation of potassium channels of postsynaptic neurons, thus causing their hyperpolarization. Moreover, opioid receptor agonists inhibit the secretion of water and electrolytes in the intestinal lumen, and this contributes to the development of the anti-diarrheal effect as well