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AUTOCOIDS: A BRIEF REVIEW

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ABSTRACT

Autacoids or "autocoids" are biological factors which act like local hormones, have a brief duration, and act near the site of synthesis. The word autacoid comes from the Greek "Autos" and "Acos". The effects of autacoids are mostly localized but large amounts can be produced and moved into circulation. Autacoids may thus have systemic effect by being transported via circulation. These regulating molecules are also metabolized locally. So the compounds are produced locally, they act locally and are metabolised locally. Autacoids can have many different biological actions including modulation of the activity of smooth muscles, glands, nerves, platelets and other tissues. Some other autacoids are primarily characterized by the effect they have upon different tissues, such as smooth muscle. With respect to vascular smooth muscle, there are both vasoconstrictor and vasodilator autacoids. Vasodilator autacoids can be released during periods of exercise. Their main effect is seen in the skin, allowing for heat loss. These are local hormones and therefore have a paracrine effect. Autacoids are chemical mediators that are synthesized and function in a localized tissue or area and participate in physiologic or pathophysiologic responses to injury. They act only locally and therefore also termed "local hormone." Autacoids normally do not function as the classical blood-borne hormones. Typically, autacoids are short-lived and rapidly degraded. **Autacoid modulators** interfere with the synthesis, inhibit the release or the receptors upon which they act. Autocoids are biological factors synthesized and released locally that play a role in vasoconstriction, vasodilation, and inflammation. These include serotonin,bradykinin, histamine, andeicosanoids. Vertebrates have evolved remarkable mechanisms for the repair and maintenance of their own tissues (i.e., "host" tissues) that simultaneously preclude the invasion and growth of non-host cells and viruses. The front line of host defense relies on the skin, mucosal surfaces, and cornea, where epithelial tissues provide not only the critical physical barrier to a constant exposure to pathogens, but also an interface with commensal microbes.[1,2] Inflammation is a major component of host defense, and a fundamental feature of this vital response is the recruitment of leukocytes to sites of injury.[3,4] Polymorphonuclear leukocytes (PMN) and macrophages in particular are essential for preventing infection and the concomitant threat of life-threatening sepsis. Indeed, in humans, vulnerability to infection is an inevitable consequence of all known genetic or acquired defects in leukocyte function, including defects in adhesion, microbial killing, and phagocytosis; deficiencies in the generation of leukocytes in the bone marrow increase rates of infection and also other illnesses and raise mortality rates.[1] In fact, any injury that compromises the external epithelial barrier triggers a robust inflammatory response.

Acute inflammation and wound healing are intimately linked responses that evolved to remove pathogens and noxious agents and ultimately restore tissue function and homeostasis. Acute wound healing and inflammation are tightly regulated responses that include highly complex programs with overlapping time course, common cell types, and shared chemical mediators.[3-8] Delineation of these two vital injury responses has posed a major challenge, particularly in regard to a definitive role for inflammation and leukocytes in the wound healing response.[5,7,9,10] Pharmacological suppression of the inflammatory response has become a major clinical target, primarily in an effort to control the precarious acti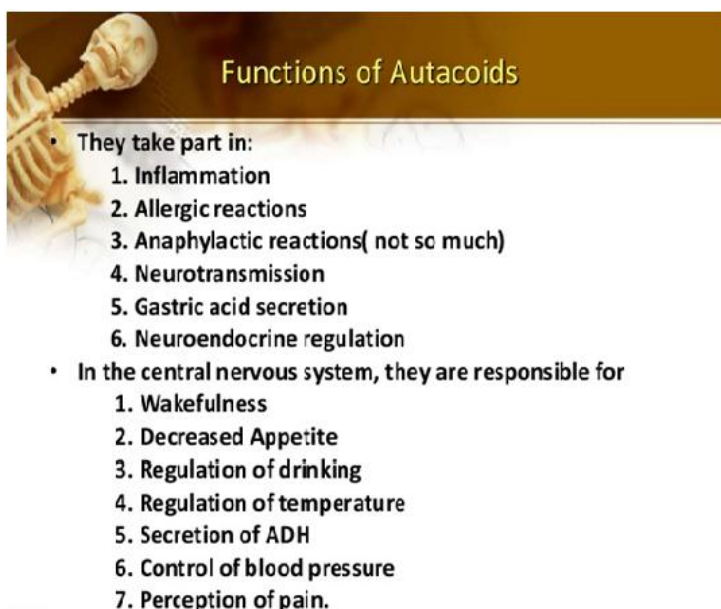vation of powerful inflammatory responses that can involve "friendly fire" (e.g., leukocyte-mediated tissue injury), a key problem in inflammatory diseases and chronic wounds. Indeed, elegant studies employing knockout and knockdown approaches provide strong evidence that exacerbated inflammation impairs wound healing see.[5,6,9] Our prevailing paradigm thus suggests that nature tends to err on the site of caution, so that responses to injury can appear overzealous, triggering inflammation and impeding wound healing. On the other hand, several tissues—such as the oral mucosa and the cornea in particular—exhibit differential injury responses that are characterized by rapid wound healing and controlled inflammation, without compromising host defense.[2,9,11,14] A key feature of these privileged tissues

upon injury is a restrained and self-resolving inflammatory response and the ability to control the precarious activation of PMN. A rapidly evolving field of research has begun to delineate endogenous circuits, depending on lipid autacoids, that restrain leukocyte responses and promote resolution of acute inflammation.[3,4,15,17] This review will focus on the emerging evidence that suggests that protective lipid autacoid circuits have a central role in privileged injury responses.

Examples of autacoids

- <u>Amines</u>: histamine, serotonin (5HT)
- <u>Polypeptides</u>: kinins, oxytocin, angiotensin II, vasopressin, atrial natriuretic factor, endothelins.
- <u>Fatty acids</u>: prostaglandins, leukotrienes, thromboxanes, platelet activating factor (PAF).
- <u>Others</u>: endothelium-derived relaxing factor (NO), cytokines (proteins).

Functions of Autacoids

- They take part in:
  1. Inflammation
  2. Allergic reactions
  3. Anaphylactic reactions(not so much)
  4. Neurotransmission
  5. Gastric acid secretion
  6. Neuroendocrine regulation
- In the central nervous system, they are responsible for
  1. Wakefulness
  2. Decreased Appetite
  3. Regulation of drinking
  4. Regulation of temperature
  5. Secretion of ADH
  6. Control of blood pressure
  7. Perception of pain.

Physiological function
1. Autacoids modulate blood flow in specific tissues.
2. Some autacoids modulate secretory processes, for example, histamine on gastric acid formation.
3. Autacoids modulate smooth muscle function.
4. Autacoids play a key role in allergy, inflammation, smooth muscle function, pain, and certain types of drug reactions (Anaphylaxis).

C. Major classes.
The autacoids to be discussed in this chapter can be divided into three categories based on their chemical structure. Not all known autacoids will be discussed and the reader should consult a standard pharmacology text for information on vasoactive intestinal polypeptide, substance P, and the cytokines.
1. **Biogenic amines**: Histamine, serotonin (5-hydroxytryptamine)
2. **Polypeptides**: Bradykinin, angiotensin
3. **Lipid-derived autacoids**

a. **Eicosanoids**. Prostaglandins, leukotrienes, thromboxane
b. **Platelet activating factor**

II. Biogenic Amines
A. Histamine
1. **Biosynthesis**. Dietary **histidine** is decarboxylated by l-histidine decarboxylase to form **histamine**.
2. **Metabolism**. Two pathways are involved in the degradation of histamine. The major degradation pathway (>50% histamine degradation) involves conversion of histamine to an inactive metabolite 1-methylhistamine by imidazole-*N*-methyltransferase. The minor pathway (25% histamine degradation) involves breakdown of histamine by diamine oxidase (histaminase) to form imidazoleacetic acid.
3. **Distribution and storage sites**. Histamine is widely distributed in tissues and its concentration and rate of synthesis varies greatly from tissue to tissue.

a. The primary tissue sites storing histamine are the **lungs**, **skin**, mucosal layer of the **stomach** and **basophils**.

(1) Food and vagal stimulation can release histamine from the stomach mucosal enterochromaffin-like (ECL) cells. The released histamine then initiates gastric acid secretion.

(2) Allergic responses in the skin and lungs are due in part to histamine release from mast cells.

b. **Mast cells** are the primary cells that store histamine where it exists in a complex with heparin sulfate and chondroitin sulfate E in storage granules. The rate of histamine synthesis and turnover in mast cells is low.

c. Histamine is also found in CNS where it may act as a neurotransmitter.

d. Many **venoms** and **insect stings** contain histamine, as well as other biologically active substances.

e. Histamine is found in the digesta where it is formed in large part by bacterial action. This histamine normally does not reach the systemic circulation since it is metabolized by enzymes in the gut wall and liver.

4. Release

a. **Immune release**. When sensitized mast cells or basophils are coupled to IgE antibodies and then exposed to the proper antigen; the mast cell degranulates, thereby releasing histamine and other autacoids. This is also referred to type I IgE-mediated hypersensitivity reaction.

b. **Drug-induced release**. Drugs, usually strong bases (morphine, polymyxin, tubocurarine, codeine, lidocaine, penicillin), and/or their vehicles are capable of releasing histamine but this release does not involve degranulation or mast cell injury. These drugs displace or compete with histamine for the binding sites with heparin.

c. **Plant and animal stings** are capable of releasing histamine, which is an important component of the physiologic reaction (erythema, pain, itch) to these stings.

d. **Physical injury** such as heat, cold, or trauma can disrupt the mast cells thereby releasing histamine.

Receptors

Four classes of receptors (H_1, H_2, H_3, and H_4) mediate the action of histamine.

a. **H_1-receptors are coupled to G_q protein–phospholipase C and mediate the following effects:**

(1) Contraction of smooth muscle and neuronal actions are due to increases in $[Ca^{2+}]_i$ and activation of protein kinase C (see Chapter 1 for detailed information).

(2) Relaxation of vascular smooth muscle involves Ca^{2+}-induced formation of nitric oxide (NO).

(3) H_1-receptors mediate contraction of bronchiolar and intestinal smooth muscle, vasodilation of small arteries and veins, increased capillary permeability and pruritus. There are considerable species variations in their sensitivity of bronchial smooth muscle to contraction by histamine. The guinea pig bronchi are the most sensitive but the bronchi of rabbit, dog, goat, calf, pig, horse, and human also contract. In contrast, histamine relaxes respiratory smooth muscle in cats (via H_1 and H_2) and sheep (via H_2). The mechanisms by which H_1-receptors mediate brochodilation in cats are not known. H_2-receptors mediate bronchodilation via an increase in cAMPlevels.

b. H_2-receptors are coupled to G_s protein-adenylyl cyclase

Stimulation of G_s-coupled H_2 receptors activate adenylyl cyclase and increase tissue cAMP levels. This is the mechanism by which vascular smooth muscle relaxes, and gastric acid secretion is stimulated.

H_2-receptor primarily mediates gastric acid secretion and vasodilatation.

(1) Agonists include 4-methylhistamine and dimaprit.

(2) H_2-Antihistaminec include: cimetidine, ranitidine, famotidine, and nizatidine. Recent evidence suggests, just like H_1-antihistamines, these drugs are inverse agonists. (Table 3-1).

c. H_3-receptors are coupled to $G_{i/o}$ protein. Inhibition of the release of histamine and other neurotransmitters involves inhibition of cAMP synthesis, opening of K^+ channels to increase K^+ efflux, and closure of Ca^{2+} channels to block Ca^{2+} entry into the nerve.

H_3-receptors are located presynaptically on neurons and inhibit neurotransmitter release. There are no drugs used in veterinary medicine that specifically activate or block these receptors.

d. H_4-receptors are coupled to $G_{i/o}$ protein and activate phospholipase C-β by Gβγ (see Chapter 1 for detailed information). These receptors are selectively expressed in mast cells, basophils, and eosinophils. Activation of H_4-receptors mediates histamine-induced mast cell chemotaxis and leukotriene B_4 production via activation of phospholipase C-β. Thus, H_4-receptors may play a role in early events of inflammation, edema, and thermal hyperalgesia.

H_4-receptor antagonists are being developed as anti-inflammatory drugs that involve mast cells and eosinophils.

6. Physiologic and pathologic roles

a. **Gastric acid secretion**. Histamine is the most important regulator of gastric acid secretion and it stimulates secretion via H_2 receptors (see below under pharmacological effects).

b. **Allergic reactions and anaphylactic shock**. The binding of antigenic substances to IgE molecules on mast cells causes the release of histamine. Other biologically active substances such as prostaglandin

D_2 and leukotrines (LTC_4 and LTD_4) are also released.

c. **Inflammation**. Histamine may be involved in the vasodilation observed in the inflammatory process.

d. **Neurotransmission**. Histamine is a neurotransmitter in various brain areas and is involved in activating sensory nerves resulting in pain and itch sensations.

e. **Microcirculation**. Histamine relaxes arterioles and increases capillary permeability.

7. Pharmacologic effects

a. **Cardiovascular system**

(1) Histamine dilates arterioles, capillaries, and venules, increases cardiac contractility and heart rate by activating both H_1- and H_2-receptors. The cardiovascular effects are complex. There is a decrease in peripheral resistance (vasodilatation), resulting in **hypotension**. The stimulation of cardiac activity involves a direct action and reflex activation of the sympathetic nervous system, which is activated by the low blood pressure.

(2) There is an increase in capillary permeability brought about by contracting the endothelial cells, which exposes the basement membrane. Fluid and protein pass across the basement membrane to produce edema.

b. **Respiratory system**. Respiratory smooth muscle is contracted in most species via H_1-receptors (see II A 5 a). There is also stimulation of glandular secretion and prostaglandin formation. Asthmatics are generally more sensitive to histamine than normal animals.

c. **Glandular tissue**. Histamine can stimulate glandular tissues to increase secretion. A most important action of histamine is its ability to increase gastric acid and pepsin secretion from the gastric mucosa via H_2-receptors.

(1) Regulation of gastric acid production is quite complex. Acid secretion by parietal cells is regulated by histamine, acetylcholine (ACh), gastrin, and prostaglandin E_2 (PGE_2).

(2) Sight and smell of food activate the vagus via the CNS to release ACh on parietal cells (M_3-muscarinic receptor) and on enterochromaffin-like (ECL) paracrine cells (M_1-muscarinic receptor).

(3) The presence of food and an increase in antral pH initiate the release of gastrin. Gastrin acts on CCK_2 receptors of the parietal and ECL cells. Histamine is released from ECL cells that are close by, and activate parietal H_2-receptors.

(4) ACh has both a direct and indirect action on gastric acid production. Activation of M_3-receptors directly activates the parietal cell, whereas activation of the M_1-receptor on the ECL cells releases histamine which in turn activates H_2-receptors on the parietal cell.

(5) Gastrin has both a direct and indirect action. Gastrin directly activates CCK_2-receptors on parietal cells to increase gastric acid secretion and indirectly increases gastric acid secretion by activating the release of histamine from ECL cells, which again in turn activates H_2-receptors on the parietal cells. Thus, **histamine release is a major factor in the stimulation of acid production by both ACh and gastrin**.

(6) Activation of H_2-receptors enhances the gastric acid secretion by ACh and gastrin on parietal cells. Upon H_2-receptor stimulation, intracellular cAMP is increased. Activation of PKA by cAMPtranslocates H^+, K^+-ATPase in tuberovesicles to canalicular membrane, which subsequently releases H^+ into the lumen. Upon stimulation of M_3-receptors and gastrin (CCK_2) receptors, calmodulin kinase is activated to translocate the H^+, K^+-ATPase to canalicular membrane as well. Chloride is released into lumen by K^+ and Cl^- carrier, evoking next increase in HCl level in the lumen

(7) H_2-antihistamines inhibit not only HCl secretion by histamine but secretion stimulated by gastrin, ACh (vagus), and food. This explains why H_2-antihistamines are effective therapy for peptic ulcers. Proton pump inhibitors (e.g., omeprazole) block the H^+, K^+-ATPase in canalicular membrane. PGE_2 act as a negative regulator of gastric acid secretion as PGE_2 activates $G_{i/o}$-coupled EP_3 receptors on parietal cells.

(8) Histamine can increase the release of catecholamines from the adrenal medulla and stimulate salivary secretion.

d. **Intradermal tissue**. Intradermal injection of histamine produces a **triple response (of Lewis)**. Insect and plant stings mimic many of these responses.

(1) A **reddening** at the site of injection is due to dilation of the small arterioles.

(2) Dilation of arterioles extends beyond injection site (**Flare**). The flare involves an axon reflex since cutting the cholinergic nerves abolishes the reflex.

(3) Swelling (**Wheal**) occurs at the injection site due to separation of the endothelial cells and edema caused by the increased capillary permeability, which is due to H_1-receptor-mediated contraction of endothelial cells.

(4) The intradermal injection of histamine causes pain and itching by stimulation of H_1-receptors on sensory nerve endings.

8. Therapeutic uses of histamine agonists

a. **Histamine phosphate** can be used for diagnostic purposes for testing of gastric acid secretion and pheochromocytoma. However, its profound side effects limit its use.

b. **Betazole** is an analog of histamine, which is an H_2-receptor agonist. Betazole has a 10-fold selectivity for stimulation of gastric acid production over vasodilation. Pentagastrin is also used for this purpose.

Figure 1. Synthesis and catabolism of histamine. Note: The conversion of imidazole acetaldehyde to

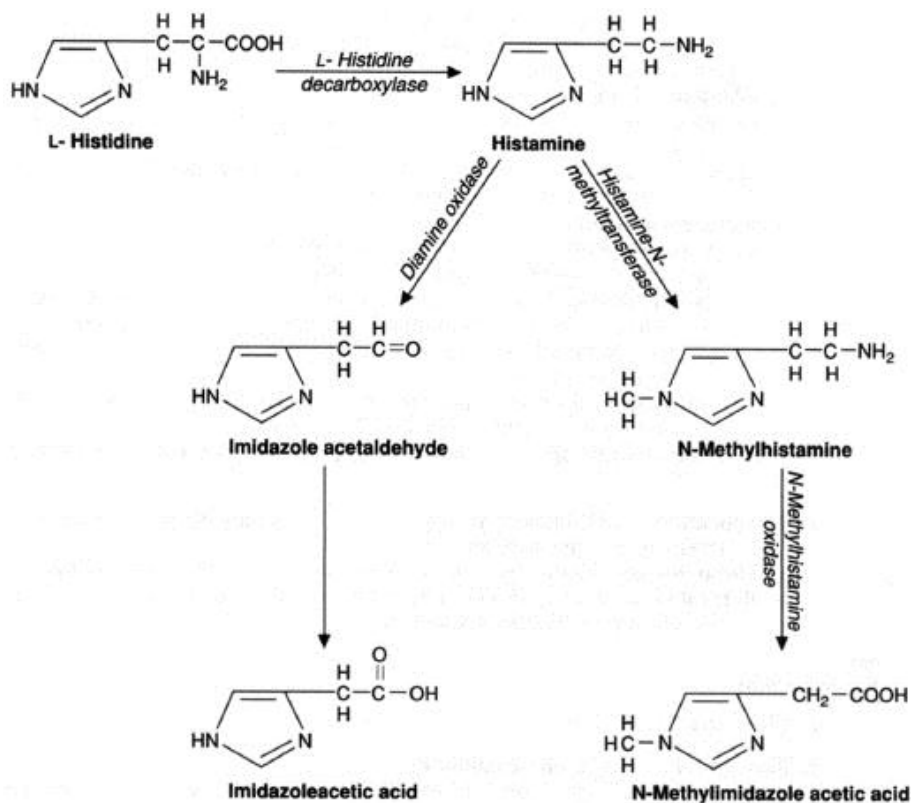imidazoleacetic acid is catalyzed by acetaldehyde dehydrogenase.

Figure 1: Histamine Pharmacology.

B. Antihistamines. Therapeutically useful antihistamine drugs are H_1-antihistamines and H_2-antihistamines. At present there are no clinically useful H_3 or H_4-antihistamines.

1. H_1-antihistamines were the first type of antihistaminic drugs discovered and are sometimes referred to as the classical antihistaminics.
a. Mechanism of action. Traditionally, it was thought that H_1-antihistamines act as competitive antagonists of histamine receptors. However, recently it has been demonstrated that most, if not all, of H_1-antihistamines act as **inverse agonists** rather than the receptor antagonists. (See Chapter 1 for detailed information on inverse agonists.).

b. Classification of H_1–antihistamines. Histamine can be broadly classified into two groups based on usage: (1) first-generation H_1-antihistamines and (2) second generation H_1-antihistamines.

Most frequently used first-generation H_1-antihistamines are **diphenhydramine, dimenhydrinate, hydroxyzyline, chlorpheniramine, meclizine, promethazine,** and **cyproheptadine**. These drugs are unionized drugs at physiological pH and easily cross the blood–brain barrier (BBB). Therefore, they produce CNS side effects, in particular, sedation.

Commonly used second-generation drugs are **loratadine (Claritin®), cetirizine (Zyrtec®), and fexofenadine (Allegra®)**. This class of drugs is ionized at physiological pH and is difficult to cross BBB.

c. **Pharmacologic** effects of H_1-antihistamines
(1) **Relaxation** of contracted bronchiolar smooth muscle.
(2) **Relaxation** of contracted intestinal smooth muscle.
(3) **Inhibition** of histamine-induced vasodilation and increased capillary permeability and thereby blocking formation of edema and wheals.
(4) **Inhibition** of itch sensation by prevention of stimulation of sensory nerves. Many H_1-antihistamines have a potent **local anesthetic action** that may contribute to their inhibition of itching and pain.

d. Other pharmacologic effects of H_1-antihistamines.
(1) **Sedation** is a common effect of first-generation H_1-antihistamines but sedation does not correlate with their potency for inhibiting H_1-receptors. Sedation may be a desirable/undesirable effect and can be expected to be additive to other CNS depressants.
(2) **Antimuscarinic effects** are prominent for some H_1-antihistamines, for example, **diphenhydramine** and **promethazine**, which decrease secretions and relax smooth muscles.

(3) Antimotion sickness (antiemetic) effects. This effect is due to the inhibition of histaminergic signals from the vestibular nucleus to the vomiting center in the medulla. All H_1-antihistamine have this effect, but some of them (diphenhydramine, dimenhydrinate, and meclizine) have more potent antimotion sickness effect than others in the group.

e. Therapeutic uses. H_1-antihistamines are administered orally, parenterally, or topically for the following conditions.
(3) Treatment of patients with allergic conditions and to reduce or ameliorate the effects due to histamine. Conditions benefited from
a. H_1-antihistamines include:
(a) Urticaria and pruritus
(b) Allergic reactions to drugs
(c) Anaphylaxis
(4) Prevention of motion sickness. Diphenhydramine, dimenhydrinate, and meclizine are more effective in preventing motion sickness than other H_1-antihistamines.
(5) Sedation induction. Promethazine and diphenhydramine are the most potent for inducing sedation.

f. Pharmacokinetics
(1) The pharmacokinetics of vast majority of H_1-antihistamines have not been studied in domestic animals. Most information is derived from humans.
(2) All H_1-antihistamines are effectively absorbed following oral administration and $T_{max} = 1–3$ hours.
(3) All H_1-antihistamines that have been studied for pharmacokinetics are well distributed and are bound by plasma proteins ($\geq 60\%$).
(4) All H_1-antihistamines are metabolized by cytochrome P450 enzymes, and these metabolites further undergo conjugation.
(5) The first-generation antihistamines are excreted primarily by the kidneys as metabolites.
(6) The second-generation antihistamines that cause least or no sedation are excreted more into feces when compared with the first-generation drugs: cetirizine (70% in urine, 30% in feces); loratadine (40% in urine, 40% in feces as metabolites); fexofenadine (11% in urine, 80% in feces).
(1) Elimination $t_{1/2}$: The $t_{1/2}$ information for animals is mostly not available.

g. Adverse effects
(1) CNS depression (lethargy, somnolence, ataxia) are the most common but they may diminish with time. The performance of working dogs may be adversely affected.
(2) Antimuscarinic effects (dry mouth, urinary retention) occur with many H_1-antihistaqmines. They should be used with caution in patients with angle closure glaucoma.
(3) In high doses CNS stimulation is possible, for example, pyrilamine in the horse.

(4) Some individuals could develop allergy to the use of H_1-antihsitamines.
(5) Drug tolerance. The decrease in efficacy and sedation (also called subsensitivity) can develop during the use of H_1-antihistamines for days or weeks. The mechanisms underlying this phenomenon are not understood.

2. H_2-antihistamines. These drugs are inhibitors of gastric acid secretion. They have little action on H_1-receptors.
a. Chemistry. H_2-antihistamines contain imidazole ring with uncharged side chains and are smaller than H_1-antihistamines. See Figure 3-2 for an example of drugs in this class.
b. Pharmacologic effects. H_2-antihistamines competitively inhibits histamine (H_2-receptors) in parietal cell and thereby decreases gastric acid production during basal conditions and when stimulated by food, vagal activity, pentagastrin, gastrin, or histamine. H_2-antihistamines have been reported to act as inverse agonists, but further validation of this observation is needed.
c. Therapeutic uses. H_2-antihistamines are administered orally to treat gastric, abomasal and duodenal ulcers, drug-induced erosive gastritis, duodenal gastric reflux, and esophageal reflux. Cimetidine is least potent among the four H_2-antihistamines. Lack of therapeutic effect of cimetidine has been reported in dogs.

d. Pharmacokinetics
(1) All four drugs are well absorbed when administered orally. T_{max} is 2–3 hours for all four drugs. The bioavailability for cimetidine, ranitidine, nizatidine, and famotidine is 95%, 81%, >70%, and 40–50%, respectively.
(2) All four drugs are well distributed in the body, with 10–20% bound by plasma proteins.
(3) Cimetidine, ranitidine, and famotidine are metabolized by cytochrome P450 enzymes. Only < 10% of nizatidine is metabolized by CYP450 enzymes.
(4) All four drugs are excreted by the kidneys as the primary route. The majority of cimetidine, ranitidine, and famotidine is excreted as metabolites and 30– 50% is excreted as the unchanged drug. A total of $\geq 60\%$ of nizatidine is excreted as the unchanged drug.
(5) Plasma $t_{1/2}$ of cimetidine, ranitidine, and famotidine are 2–3 hours for all three drugs. The $t_{1/2}$ for cimetidine and ranitidine in dogs are 1.3 hours and 2.2 hours, respectively. Plasma $t_{1/2}$ of nizatidine is 1–2 hours in humans; no information is available for animals.

e. Adverse effects are uncommon when recommended dosages are used. Cimetidine possesses weak antiandrogenic activity and can cause gynecomastia and

decreased libido in humans. The antiandrogenic effect is, in part, due to decreased testosterone synthesis.

Ranitidine, famotidine, and nizatidine seem to be very well tolerated. Rarely, agranocytosis has been seen with the use of ranitidine and famotidine.

f. Drug interactions. Cimetidine can inhibit the hepatic cytochrome P450 enzymes. It may reduce the metabolism of other drugs, which undergo hepatic metabolism, thereby elevating and prolonging their concentration in the plasma.

3. Inhibitors of histamine release. The one drug in this category, cromolyn sodium, differs in mechanism of action from the H_1- and H_2-antihistamines discussed above.

a. Cromolyn sodium inhibits the release of histamine and other autacoids from mast cells. It **does not** inhibit H_1- and H_2-receptors, but opens chloride channel to hyperpolarize the cells.

(1) It is primarily used to treat pulmonary and nasal allergic reactions.
(2) It is not well absorbed from the gut and has no clinical use when given orally.
(3) It is used in a prophylactic manner.
(4) It has been used in the horse where it is nebulized and delivered via a face mask.
(5) The 4% eye drop is used to control allergic conjunctivitis.

CONCLUSION

Controle responses to epithelial and epidermal injury appear to rely on redundant circuits that tightly control the precarious, but essential, activation of the inflammatory processes. Anti-inflammatory lipid autacoids, have emerged as central regulators of leukocyte function and the active resolution of inflammation.

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