

ANTIINFLAMMATORY and ANTIALLERGIC Therapy

ANTIHISTAMINES and GLYCOCORTICOIDS



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INFLAMMATION

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graph TD; A[INFLAMMATION] --> B[ACUTE]; A --> C[CHRONIC]
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ACUTE

Importance:

Elimination of exogenous dangerous compounds
including molecules in microbes
deliberating reactive oxygen radicals ==>

CHRONIC

tissue damage

I. Innate immune responses

1. phase: acute vascular
2. phase: subacute cellular

3. chronic proliferative

Autoaggressive immune response
aggressive macrophages

II. adaptive immune responses

pathologically stimulated B and T ly
Cytokines IL-1,2,3
TNF alpha

Innate immune response

1. Phase

ACUTE VASCULAR

PAMP (pathogen-associated molecular patterns)

Antigens+ antigen-presenting cells

Proinflammatory cytokines:

IL-1
TNF-alpha

Dilatation in arterioles and venules

Stimulation of the proteolytic cascades

Vasodilatation
Increased permeability

2. Phase

SUBACUTE CELLULAR

endothel NO, PAF, PGI

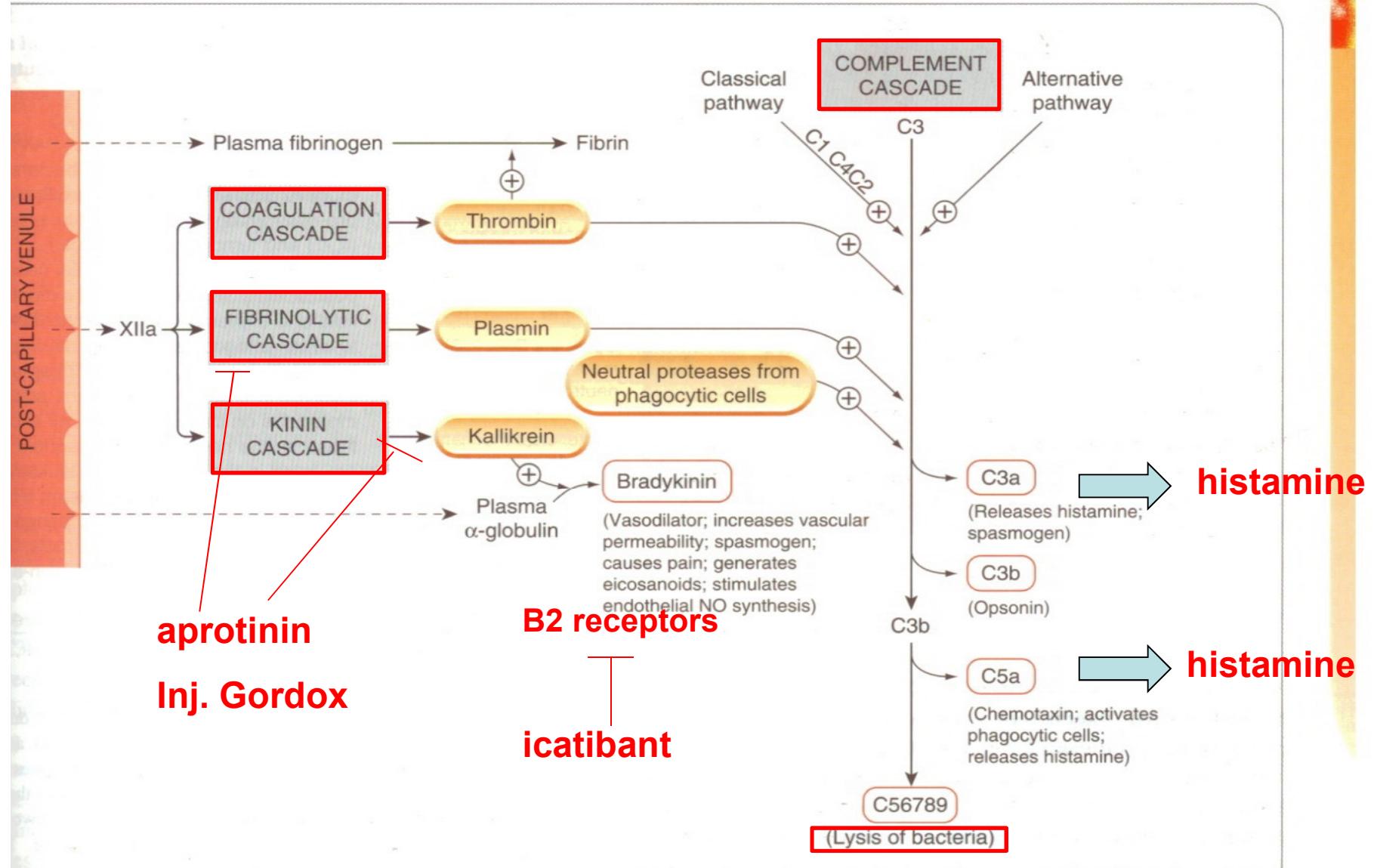
mastocytes histamin, leukotrienes
Serotonin, PGD2, PAF

Macrophages in tissues LTB4, NO
cytokines

thrombocytes PAF, ThromboxanA2

Neurons tachykinines, CGRP

pain



5.1 Diagram showing the four enzyme cascades that are activated when plasma leaks out into the tissues as a result of increased vascular permeability in an area of inflammation. Factors causing exudation are depicted in Figure 15.2. Mediators listed are shown in red-bordered boxes. Complement components are indicated by C1, C2, etc. When plasmin is formed it tends to increase kinin formation and decrease the coagulation cascade. (Adapted from: Dale et al. 1994.)

DRUGS REACT on RECEPTORS of HISTAMINE and SEROTONIN

histamine and serotonin:

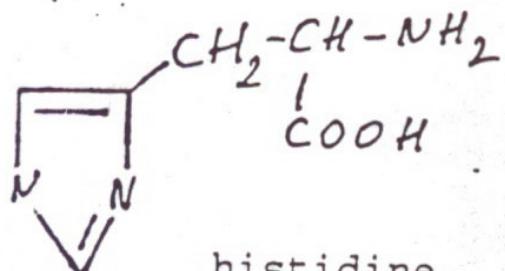
autacoids = local hormones
neurotransmitters

HISTAMINE

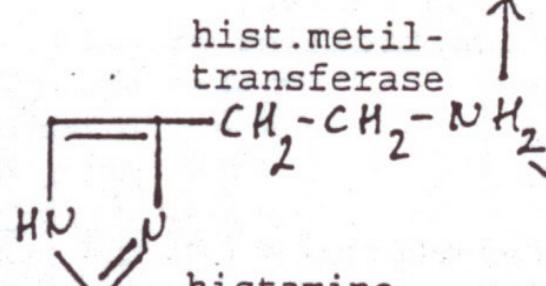
FORMATION

ELIMINATION

MAO



histidine



histamine
hist.decarboxylase
(piridoxalphosphate)

DAO

imidazole-
acetic acid

URINE

Distribution of histamine in central nervous system:

Associated with synapsis

in thalamus
hypothalamus
cerebellum
forehead lobe

A great amount of histamine can be found in the cerebrospinal fluid.

As a neurotransmitter influences through H_1/H_2 receptors

intake of fluid
ADH secretion
controlling of
weight
blood pressure
pain sensory.

Distribution of the H₃ receptors:

Especially in the presynaptic membrane

They inhibit releasing of histamine by negative feed back similar to the function of alfa₂ receptors (1987, Arrang).

H₃ receptor agonist: alfa-metilhistamine

H₃ receptor antagonist: impropidine, thioperamide

Drug candidates in experimental stages

H3 antagonists/inverse agonists: for obesity

sleep disorders

cognitive disorders

tiprolisant a selective H3 inverse agonist:

reduces sleep cycles in narcolepsy

H2 antagonist. burimamide:

in CNS on H2 receptors it has analgesic effect

without any dependence,

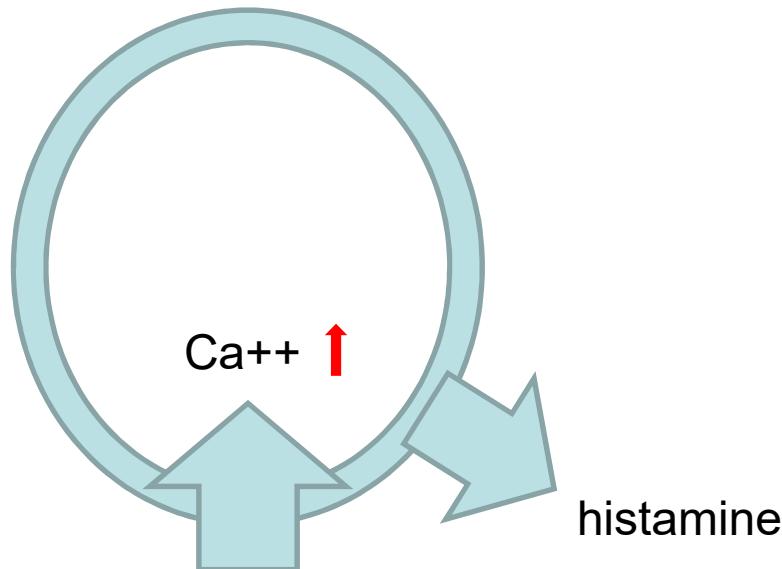
or respiratory depression

Histamine receptors

	H ₁	H ₂	H ₃	H ₄
distribution	smooth muscle endothelium nerve endings	gastric mucosa cardiac muscle mastocytes brain	presynaptic: brain enteral plexus, other neurons	White blood cells
	bound to G protein			
postreceptorial mech.	↑ IP ₃ , DAG ↑ Ca ⁺⁺ NF-κB	↑ cAMP ↓ Ca ⁺⁺	N type Ca channels ↓ Ca ⁺⁺	IP ₃ MAPK
physiologic or pathologic effects	oedema ↓ RR bronchoconstriction urticaria itching	↑ gastric acid secretion ↑ contractility ↑ pacemaker activity (palpitation)	neg. feed back in CNS	myelopoiesis Chemotaxis for eosinophils basophils mastocytes

HISTAMINE RELEASE FROM MASTOCYTES

NONRECEPTORIAL



Base-type molecules:

Morfine
Tubocurare
Vancomycine
Polymyxine
Bradikinine
P substance

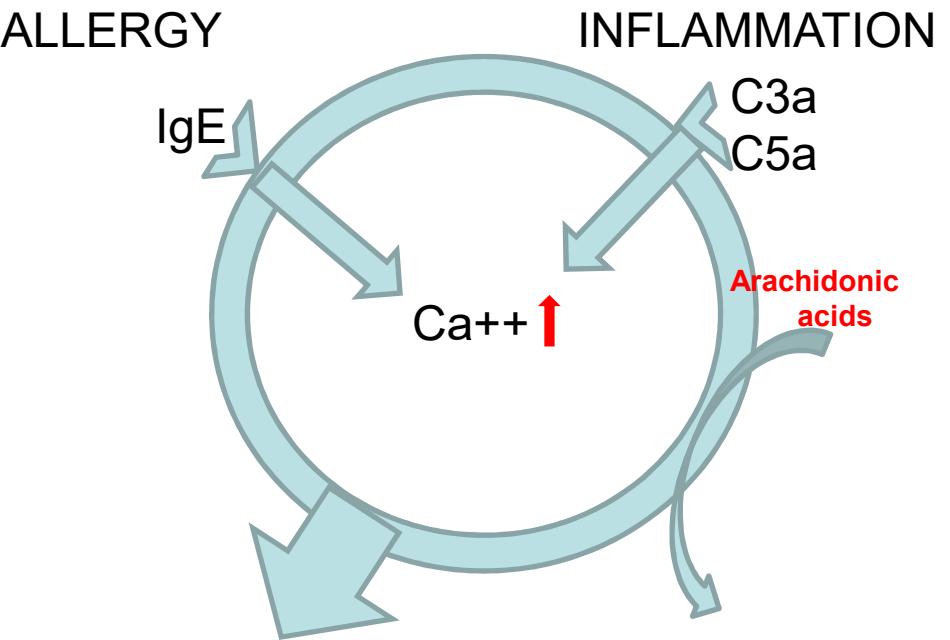
IN IMMUNE RESPONSES

ALLERGY

IgE

↑

Ca⁺⁺



Histamine
Bradikinine
serotonin

Prostaglandins
leukotrienes

Vasodilatation
Permeability ↑

Histamine release plays role in the following syndromes:

I. type, IgE mediated hypersensitivity as:

anaphylactic shock

asthma bronchiale

angioedema

allergic rhinitis/conjunctivitis

allergic reactions: urticaria

itching

mastocytosis = urticaria pigmentosa

histamine-release caused by drugs, toxins (e.g. snake, spike, bee)
inflammation, regeneration

"cold" - inflammation, mucosal swelling (antihistamines are often used for preventing sinusitis maxillaris, otitis media)

ulcus pepticum

carcinoid sy

some kind of headaches

Clinical uses of histamine and its analogues:

mostly in provocative diagnostic tests:

1. for testing of secretion of gastric acid (selective H₂ agonist e.g. betazole=Histalog)
2. diagnosis of phaeochromocytoma
3. Pulmonary function testing for evaluating bronchus hyperreactivity

Antagonist effects are used in clinical practice.

1. Drugs inhibit histamin relase: cromoglycate sodium,
nedocromil
2. Physiological antagonists: epinephrine, noradrenalin
3. Histamine receptor antagonists/inverse agonists

H₁ receptor antagonists

chemical structure				
general structure:	clinical indication for all H ₁ blockers			
subgroups	prototypes	other effects	special clinical uses	side effects
1. ethylenediamine derivatives	chloropyramine = Suprastin antazoline	antimuscarinic vasoconstriction	eye drops in combinations for conjunctivitis	marked sedation gastrointest drying of mouth mucosa
2. ethanolamines	dimenhydrinate = Daedalon diphenhydramine = Benadryl doxylamine = Bendectin	antimuscarinic marked anti-motion sickness activity marked local anaesthetic effect marked sedation	prevention of motion sickness vertigo local anaesthesia sedatohypnoticum	marked sedation antimusc. perhaps doxylamine is teratogenic
3. phenothiazine derivatives	promethazine = Pipolphen ----- mequitazine = Primalan	antiemetic sedation local anaesthetic antimuscarinic	vomitus vertigo local anaesth.	marked sedation photosensitive reactions extrapiramidal symptomes ----- moderate sedation
4. alkylamines	dimethindene = Fenistil			slight sedation excitation

First generation H1 receptor inhibitors with therapeutical effects on CNS

H1 antagonist effect ——————> Ach release inhibition

Therapeutical use:

Active ingredient	brand name	effects	clinical use	side effects
hydroxyzin	Atarax	H1+5-HT2A, D2 alfa1 antagonist	anxyolitics sleep aid	dyskinesy >1 year th.
Doxepin	Hyperlex	dibenzoxepin tricyclic comp. H1 +antimuscarin+ monoamine reuptake inhibitor	sleep aid	
Doxylamine	Bendectin		sleep aid	maybe teratogenic

subgroups	prototypes	other effects	special clinical usage	side effects
5. piperazine derivatives	oxatomide = Tinset cetirizine = Zyrtec	stabilizing mastocytes	asthma br. prophylaxis	some are teratogen in rodents
6. piperidines derivatives 2nd generation	terfenadine = Teldan astemizole = Hismanal	long $T_{1/2}$, 2x/day ^{terfenadine} 1x/day	do not cross blood-brain barrier the least sedation	ventricular arrhythmias
7. miscellaneous	ciproheptadine = Peritol, Periactin clemastine = Tave-gyl ketotifene = Zaditen loratadine = Claritine	effect on + serotonin rec. inhibits several mediator release 1x/day	improvement of appetite asthma br. prophylaxis	moderate sedation slight sedation moderate sedation slight sedation
2nd generation	pizotifene = Sandomigran setastine = Loderix tenalidine = Sandosten-Ca	effect on + serotonin rec.	therapy of migraine	slight sedation slight sedation depression of bone marrow

Interactions with other drugs:

alcohol, sedatohypnotics, neuroleptics

MAO inhibitors, atropine, tricyclic antidepressants

ketoconazole, itraconazole, macrolid antibiotics, grapefruit juice

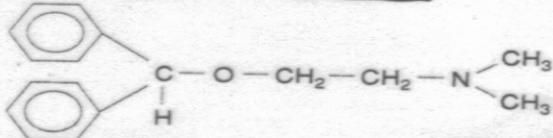
enhancement of CNS depression

enhancement of antimuscarinic effects

intox., dangerous arrhythmias

Piperphen promedazin

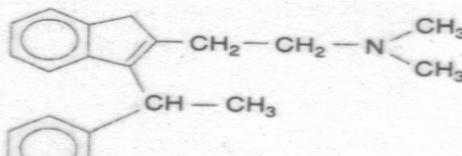
H₁-receptor-antagonisták



Daedalon

diphenhydramin

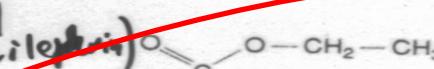
Benadryl



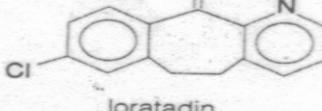
Fenistil

dimetinden

Vibrocil
(+phenylephrin)

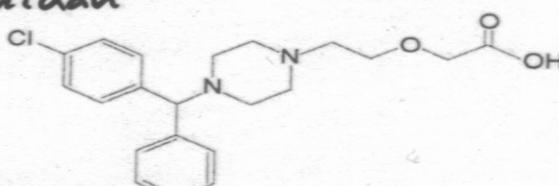


Claritine
Erolin
Flonidan



loratadin

Zyrtec



cetirizin

Telfast

texofenadin

45.1. ábra. A hisztamin és néhány H₁-, illetve H₂-receptor-ant.

hisz

CYP3A4

desloratidin
Aerius

2nd generation of
H1 receptor
antagonists

They inhibit
IL-1, TNF α , GM-CSF

ICAM-1

In **anaphylactic shock** a huge amount of released histamine results in drop of blood pressure suddenly, which is the leading symptom. However not only histamine but also many other inflammatory mediators are liberated.

THERAPY of ANAPHYLACTIC SHOCK

to stop exposition

1st step: epinephrine subcutaneously, then if it is required intravenously

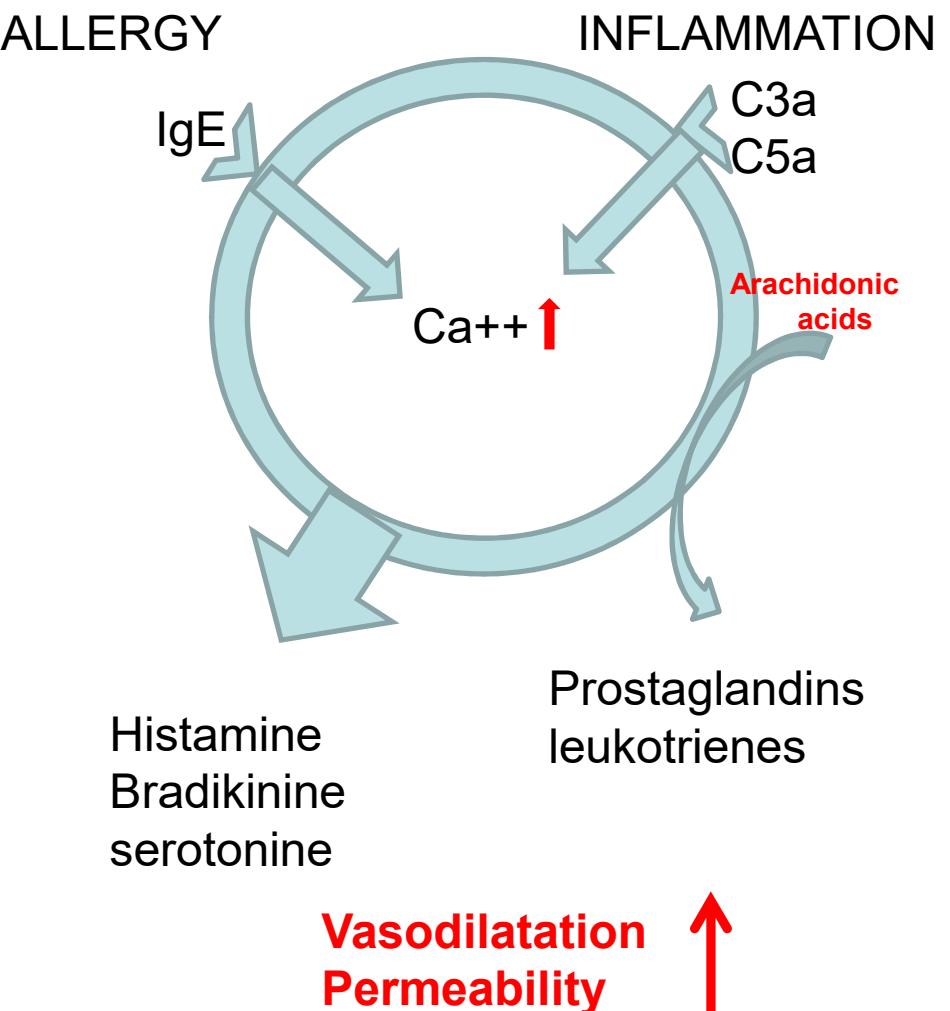
2nd step: glucocorticosteroids intravenously

3rd step: H1 receptor blocking drugs intravenously

ANTIINFLAMMATORY AND ANTIALLERGIC TREATMENT WITH GLYCOCORTICOSTEROIDS IN CLINICAL PRACTICE

LEUKOTRIENE RELEASE FROM mastocytes and other leukocytes through arachidonic acid pathway

IN IMMUNE RESPONSES



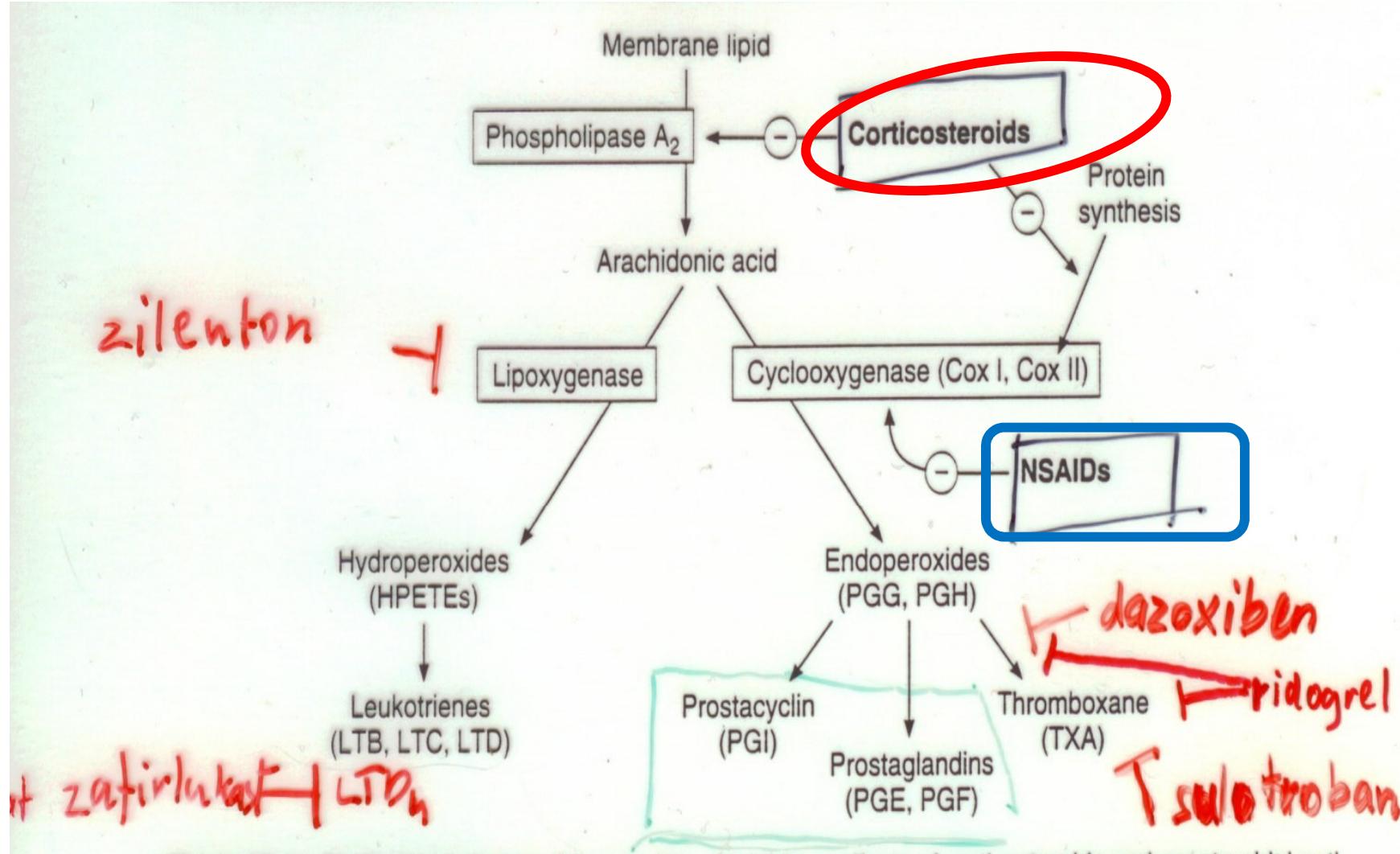


Figure 18-1. Synthesis of eicosanoids and sites of inhibitory effects of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).

Katzung et al Basic and Clinical Pharmacology textbook

Effects of Glucocorticoids

They inhibit each step of inflammation :

acute vascular, subacute cellular
and the chronic inflammation with proliferative phase

Inhibition of neutrophils, mastocytes to pass through vessel wall into the perivascular space

Inhibition of Th lymphocytes , the clonal proliferation
and the Th1/Th2 switch

Inhibition of fibroblasts in production of collagen and glikoaminoglikan

Side effects.

many in long-term therapy

e.g. immunosuppression, inhibition of wound healing

inhibition of osteoblasts + increase in osteoclast activity


osteoporosis

Table 60–3
Effects of Glucocorticoids on Components of Inflammatory/Immune Responses

CELL TYPE	FACTOR	COMMENTS
Macrophages and monocytes	Arachidonic acid and its metabolites (prostaglandins and leukotrienes)	Inhibited in part by glucocorticoid induction of a protein (lipocortin) that inhibits phospholipase A2.
	Cytokines, including: Interleukin (IL)-1, IL-6, and TNF- α	Production and release are blocked. The cytokines exert multiple effects on inflammation (e.g., activation of T cells, stimulation of fibroblast proliferation).
	Acute phase reactants	These include the third component of complement.
Endothelial cells	Endothelial leukocyte adhesion molecule-1 (ELAM-1) and intracellular adhesion molecule-1 (ICAM-1)	ELAM-1 and ICAM-1 are intracellular adhesion molecules that are critical for leukocyte localization.
	Acute phase reactants	Same as above, for macrophages and monocytes.
	Cytokines (e.g., IL-1)	Same as above, for macrophages and monocytes.
	Arachidonic acid derivatives	Same as above, for macrophages and monocytes.
Basophils	Histamine Leukotriene C4	IgE-dependent release inhibited by glucocorticoids.
Fibroblasts	Arachidonic acid metabolites	Same as above for macrophages and monocytes. Glucocorticoids also suppress growth factor-induced DNA synthesis and fibroblast proliferation.
Lymphocytes	Cytokines (IL-1, IL-2, IL-3, IL-6, TNF- α , GM-CSF, interferon gamma)	Same as above for macrophages and monocytes.

Clinical use of glucocorticoids

Glucocorticoids are the most powerful antiinflammatory drugs

Life-saving drugs in emergency
in acute allergic reactions:

anaphylactic shock
edema of epiglottis
asthma bronchiale attack
capillary leak sy in cytokine therapy

in acute shubs of the autoimmune diseases

generalized edema based upon immune reactions

Other therapeutic effects:

Immunosuppressive effects in autoimmune diseases

Antiproliferative drugs in certain malignant diseases, e.g. ALL

(d) Unwanted effects

Iatrogenic Cushing's syndrome

Plethoric
moon face

Euphoria

Buffalo hump

Hypertension
(sometimes)

Abdominal fat

Thinning
of skin

Easy bruising

Thin limbs

Poor wound
healing



	hatástartam	Relatív		
		glucocorticoid gyulladáscsökkentő	mineralocorticoid Na^+ visszatartó	lokális
		hatás (cortisolhoz viszonyítva)		
cortisol (hydrocortison)	R	1	1	1
cortison	R	0.8	0.8	0
aldosteron	R	0	500	0
prednisolon	K	4	0.8	4
methylprednisolon	K	5	0.5	5
Triamnicolon	K	5	0	5
Betamethason	H	25	0	10
dexamethason	H	25	0	

R= rövid

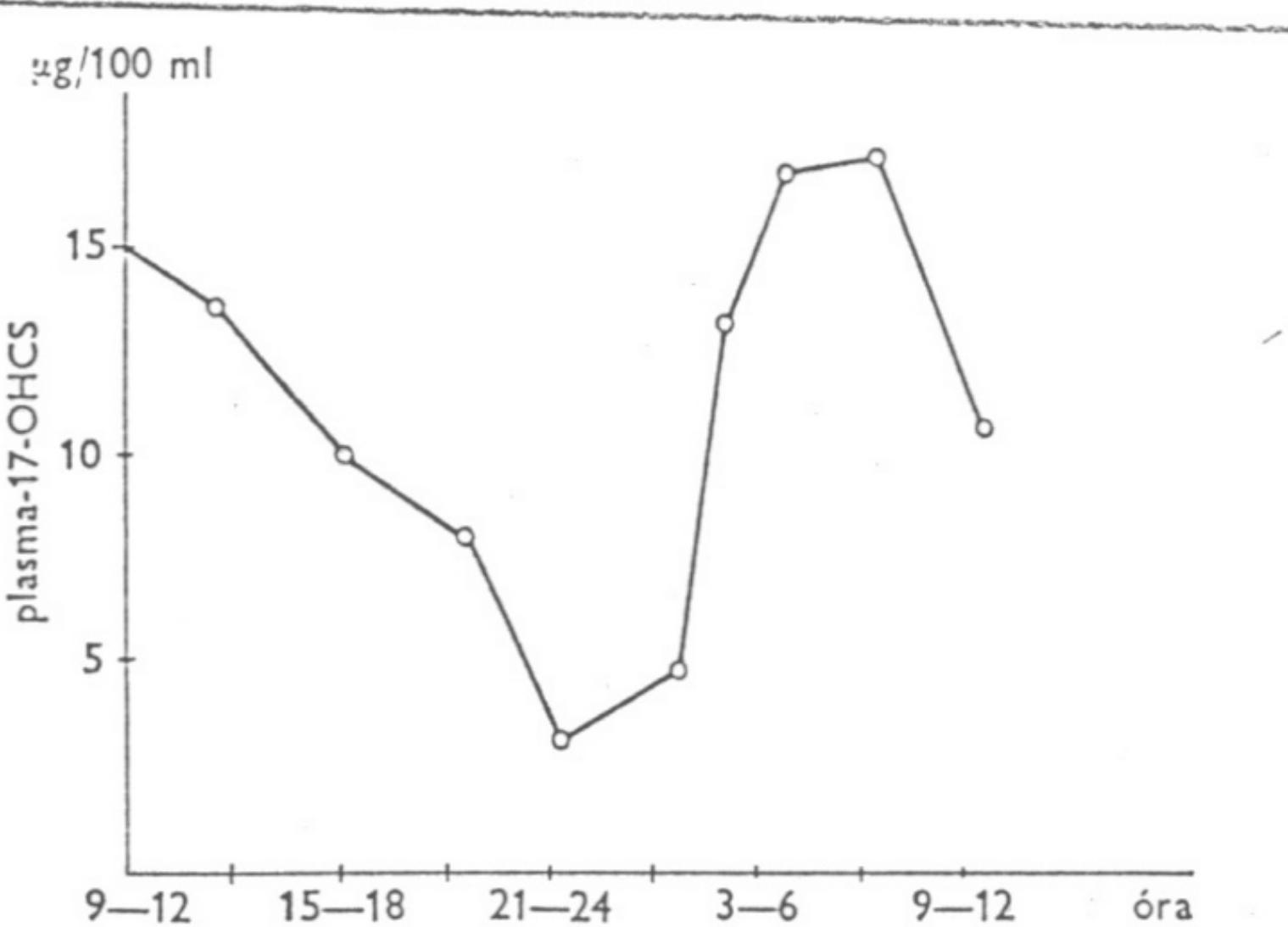
K= közepes

H= hosszú

T_{1/2} = 8-12 h vagy 20 perc az aldosteron esetében

T_{1/2}=12-36 h

T_{1/2}=36-72 h



Circadian rythm of cortisol synthesis