NATIONAL UNIVERSITY OF PHARMACY
Department of Pharmacology

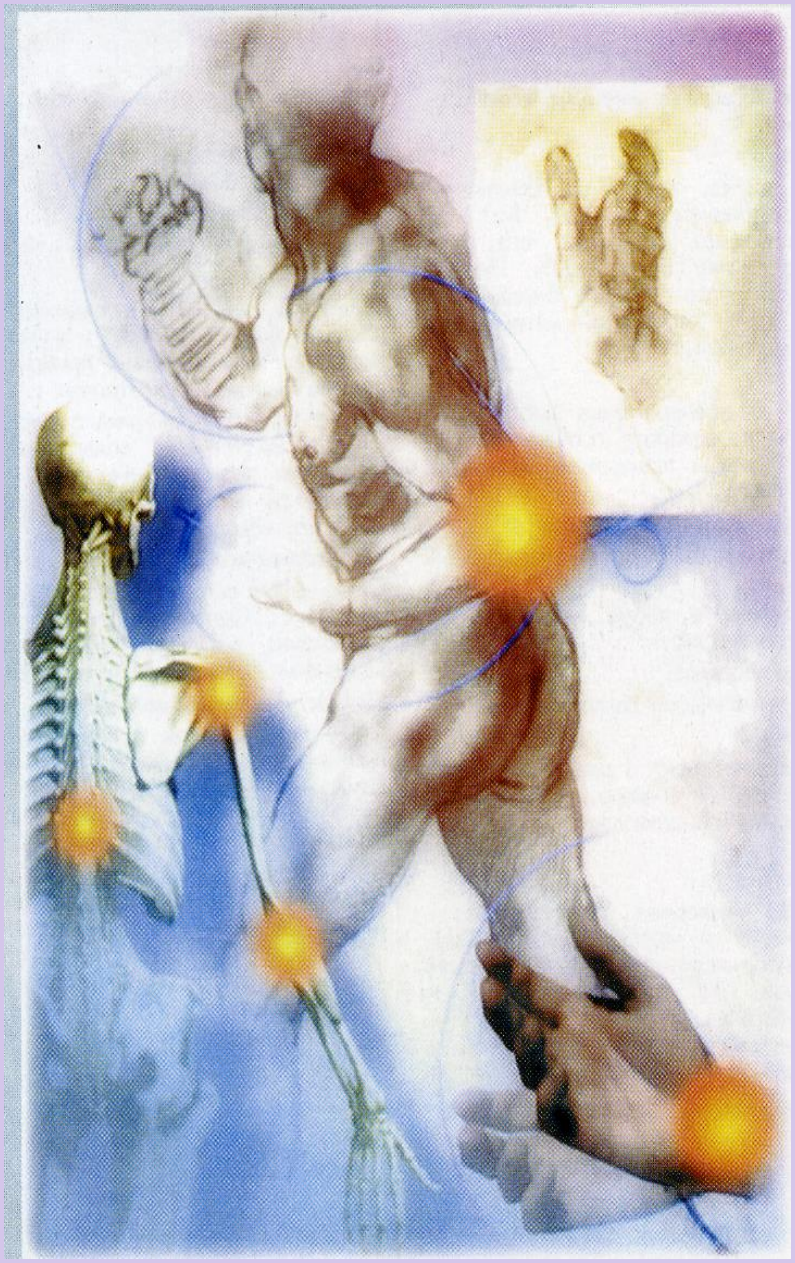
Lecture topic:

PAIN
PHARMACOCORRECTORS

1. Opioid analgesics (OA)
2. Nonopioid analgesics (NOA)
4. NSAIDs

Pain is a signal about the danger for the organism. At the same time, it causes discomfort, decreases the quality of life, may cause a pain shock

Pain is an universal response of the organism to damage, inflammation, ischemia, hunger and other patho-logical processes. It is the important protective mechanism, a signal of «not well-being» in the organism, the most frequent display of a pathology



Nociception is pain sensation.

Receptors of pain are nociceptors, there are 25-45 % of nociceptors among all receptors in the organism. The density of receptors is from 30 000 to 40 000 on 1 cm^2. The greatest density is in tooth tissues.

Thalamus is the main collector of pain impulses.

Alcohol, opium and cannabis were used as pain killers before.

PAIN PHARMACOCORRECTORS

	General anesthetics	Opioid analgesics (OA)	Non-opioid analgesics (NOA)
The mechanism of action	↓ CNS (consistently)	↓ CNS by stimulation of opioid receptors (OR)	↓ CNS (↓ COX → ↓ Pgg)
Pharmaco-dynamics (effects)	Narcotic (I-IV stages)	↓ severe pain ↓ cough, ↓ respiratory, emetic centers	↓ mild pain, antipyretic, anti-inflammatory
Indications	General anesthesia	Severe pain (that is dangerous for life)	Pain that is not dangerous for life, fever, inflammatory diseases

History of Opioids

- Opium is extracted from poppy seeds (Papaver somniferum)
- Is used for thousands years to produce:
  - Euphoria
  - Analgesia
  - Sedation
  - Relief of diarrhea
  - Cough suppression

History

- Opium and laudanum (opium combined with alcohol) were used to treat almost all known diseases
- Morphine was isolated from opium in the early 1800's and since then has been the most effective treatment for severe pain
- Invention of the hypodermic needles in 1856 produced drug abusers who self-administered opioids by injection

Glossary

- “Opium” is a Greek word meaning “juice” or the exudate from the poppy
- “Opioid” is a natural or synthetic drug that binds to opioid receptors producing agonist effects
- Damage causing (nociceptive) stimuli can be ***mechanical, thermal and chemical***

Physiological role of Nociceptive system

- **Painful sensation** is perceived by special receptors, which are called **«nociceptors»** (from Latin ***noceo*** is damage).
- **Pain mediators** (algogens) that affect nociceptors: catecholamines (epinephrine, norepinephrine and dopamine), acetylcholine, substance P, bradykinin, histamine, serotonin. Prostaglandins (Pg E_2) increase nociceptor sensitivity to chemical and thermal stimuli.
- **Impulses**, caused by painful stimuli, spread along fibres and enter the posterior horn of the spinal cord. They are transmitted up to the higher CNS centers – **thalamus, reticular formation, hypothalamus and cerebral cortex.**

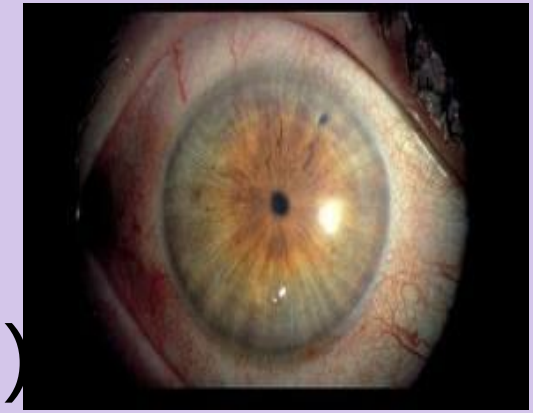
Physiological role of Antinociceptive system

- **Opioid receptors (OR)** and their ligands (ligo- means to connect). OR take part in the inhibition of pain, ↓ of stress, regulation of sleeping and emotional behavior.
- **Endogenous ligands of OR** (encephalins and endorphins) connect the receptors and inhibit the release of algogens and decrease the pain impulse transmission to the CNS.

- **Opioid receptors**: μ (mu), χ (kappa), σ (sigma), δ (delta), ε (epsilon).

μ -receptors provide:

- Analgesia
- Sedation
- Euphoria
- Physical and psychological dependence
- Inhibition of the pain, respiratory and cough centers
- Bradycardia
- Miosis (pupil constriction)
- Decrease the motility of the GIT



μ- and χ- receptors stimulation

Response	μ -1	μ -2	χ
Analgesia	★	★	★
Respiratory depression		★	
Euphoria		★	
Dysphoria			★
Decrease of GIT motility		★	
Physical dependence		★	

The mechanism of action of OA

- OA stimulate all the types of opioid receptors
- They have high affinity to μ-receptors and some effect to other OR
- OA bind to OR and activate the endogenous antinociceptive system. Because of binding to OR in the CNS, they cause inhibition of the algogens release on the hole way of the pain transmission.

Classification of OA

*Natural and semisynthetic**	*Synthetic*	
Morphine **Codeine** **Omnoponum** **Codeine phosphate*** **Aethylmorphine h/chl***	**Fentanil** **(or Fentanyl)** **Trimeperidin (Promedol)** **Piritramide (Dipidolor)** **Tilidine (Valoron)** **Buprenorphine** **Pentazocine**	**Sufentanil** **Dimenoxadol** **Butorphanol** **Tramadol**

Naloxone, Naltrexone are blockers of opioid receptors. The are antagonists of OA.

Indications:

Naloxon *– for treatment of acute poisoning with OA*

Naltrexon *– for treatment of opioid dependence*

Pharmacological “face" of OA

Medicines	Analgesia	Duration of action (hours)	↓ respiration	Addiction
Morphine (M)	standard	6	++	++
Fentanil	200 times > M	0,5	+++	++
Buprenorphine (agonist-antagonist)	20-30 times > M	6	±	±
Butorphanol (agonist-antagonist)	3-5 times > M	6	+	±
Piritamid	2 times > M	6	±	+
Trimeperidin	= M	4	+	+
Codeine	< M	6	+	±
Pentazocine (agonist-antagonist)	< M	5	±	±
Tramadol	< M	9	-	±

Pharmacological Effects of OA

Inhibitory effects	Stimulating effect
Central	
Inhibition of pain	Euphoria
Sedative and hypnotic effect	Miosis
Inhibition of the respiratory center	Stimulation of the vagal centers
Inhibition of cough center	Increase in prolactin and antidiuretic hormone production
Slight inhibition of the thermoregulation	Stimulation of receptors of the trigger zone of the vomiting center
Peripheral	
Inhibition of gastric motility and peristalsis of the intestine	Increase in the tone of the gastrointestinal tract sphincters
Inhibition of secretion of the gastric glands, pancreas and intestine	Increase in the tone of the intestinal muscles
	Increase in the tone of bronchial muscles
	Increase in the tone of bladder sphincters

Pharmacological effects of OA

- Sedation (due to inhibition of the cortical neurons)
  - Drowsiness
  - Apathy
  - Cognitive disorders
  - Sense of tranquility

- Inhibition of respiration
  - Main cause of death of opioid overdose
  - Combination of opioids and alcohol is especially dangerous

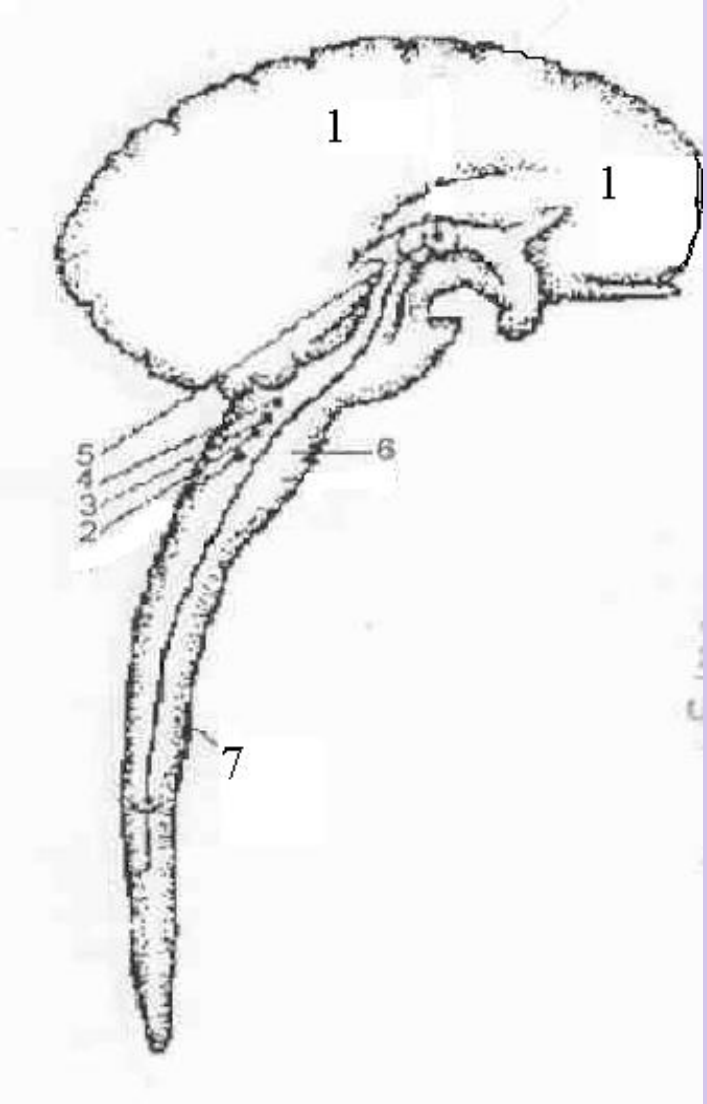
- Cough suppression
  - Opioids suppress the “cough center” in the medulla oblongata

- Constriction of pupils (miosis)

Pharmacological effects of OA

- Nausea and vomiting
  - Stimulation of receptors in the area of the medulla oblongata called the chemoreceptor trigger zone causes nausea and vomiting
- Gastrointestinal symptoms
  - Opioids relieve diarrhea as a result of their direct actions on the intestines
- Other effects
  - Opioids can release histamine causing itching or more severe allergic reactions including bronchoconstriction (in case of abstinence)
  - Opioids can affect white blood cell function and immune function

Pharmacodynamics of Morphine



Morphine inhibits the centers of:

1. Pain sensitivity
2. Cough
3. Respiratory

Morphine stimulates the centers of:

4. Oculomotor nerve (miosis)
5. Stimulation of the vagus nerve (bradycardia, the increase of the smooth muscles tone of the GIT and bladders, spasm of the sphincters)

Pharmacological characteristics of OA

Pharmacodynemics (effects)	Indications
Analgesic	**Severe pain: traumas, myocardium infarction, massive burns, surgeries, malignant tumors, severe inflammatory processes, colics, prevention of traumatic shock, premedication, neuroleptanalgesia**
Antitussive (anticough)	**pneumothorax, pulmonary bleeding; persistent strong dry cough**
Inhibition of the respiratory centre	**Acute pulmonary edema**
Stimulation of the vagus nerve	**X-ray study of the GIT**
Stimulation of the oculomotor nerve (miosis)	**Diagnostics of poisoning by Morphine and other opioids**
Side effects	**Contraindications**
Dependence (physical, psychological), abstinence, bradicardia	**Chronic pains**
Inhibition of the respiration	**Pregnancy, labour, lactation, craniocerebral trauma, hemorrhagic stroke, children under 2 years old, patients over 60 years old**

Glossary

Neuroleptanalgesia is a method of general analgesia. It is obtained by combined administration of neuroleptics, for example, **droperidol,** and active opioid analgesics **(fentanyl).** At the same time antipsychotic (neuroleptic) effect is combined with marked analgesia. Consciousness is preserved

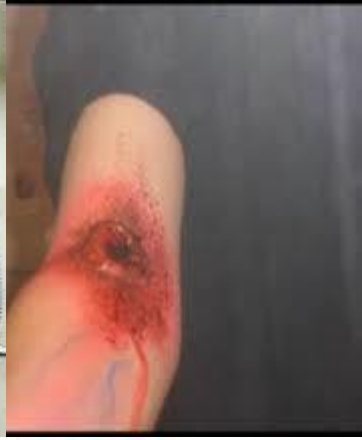
Overdose of OA leads to acute poisoning. This is marked with a loss of consciousness progressing into coma. At the same time respiration is depressed, bradycardia up to heart stoppage occur. Skin is pale, cold, and the mucous membranes are cyanotic. One of the diagnostic signs of opioid intoxication is marked miosis. Body temperatura is fallen. Lethal outcome occurs from respiratory paralysis.

In case of overdose by OA Naloxone is used.

With repeated intakes of OA tolerance to them develops. This is why drug abusers need to increase the dose of these drugs to reach euphoria.

Euphoria is mental and emotional condition in which unpleasant emotions and tiredness are eliminated, good mood, happiness, excitement, and joy appear.

Abrupt stoppage of administration of OA results in withdrawal syndrome and abstinence. Fear, anxiety, depression and insomnia appear.

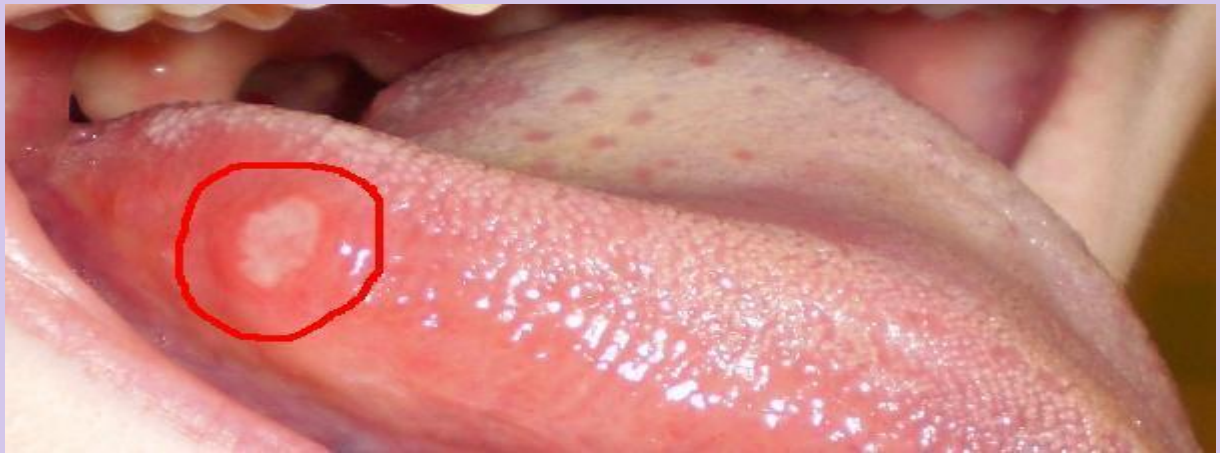


STOP

narcotics

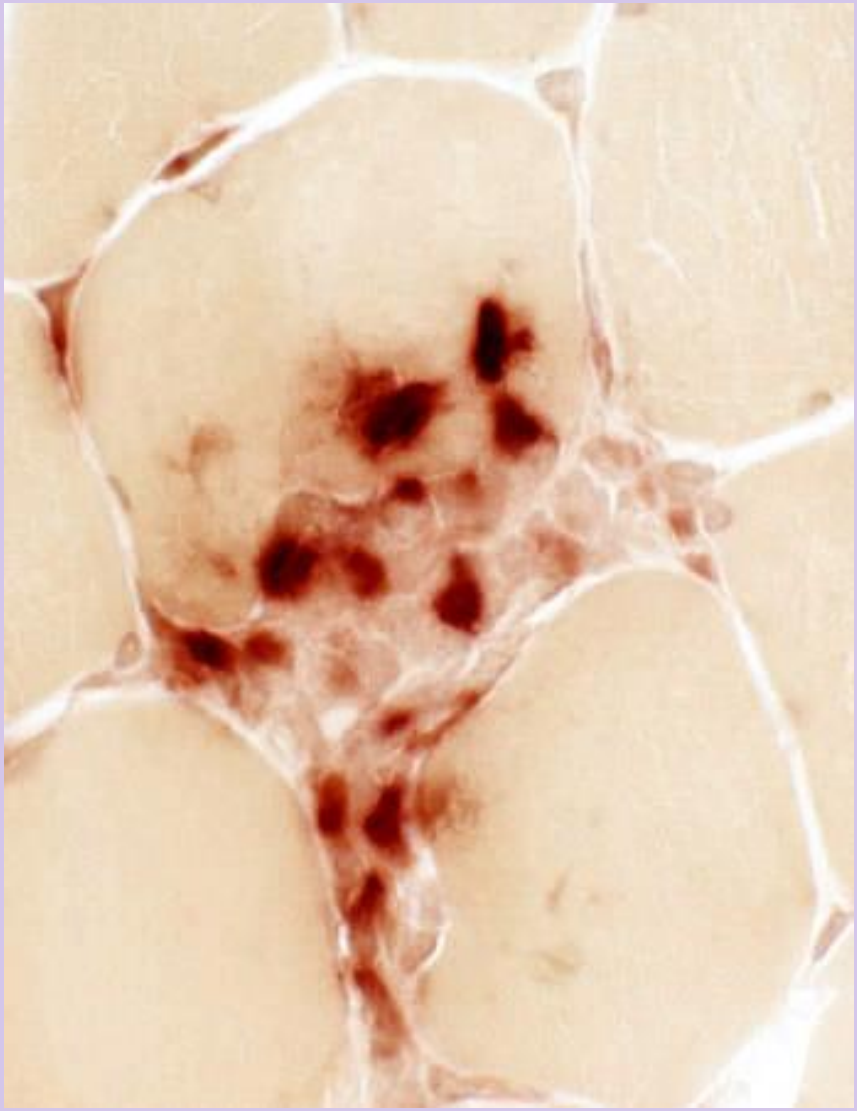
Inflammation is a universal response of the body to the influence of various exogenic and endogenous damaging factors (bacterial, viral, parasitic infections as well as allergens, physical and chemical stimuli) with complex of changes in the vascular wall, blood system and connective tissue that are directed to isolate and eliminate the injuring agent and restore (or replace) damaged tissues.

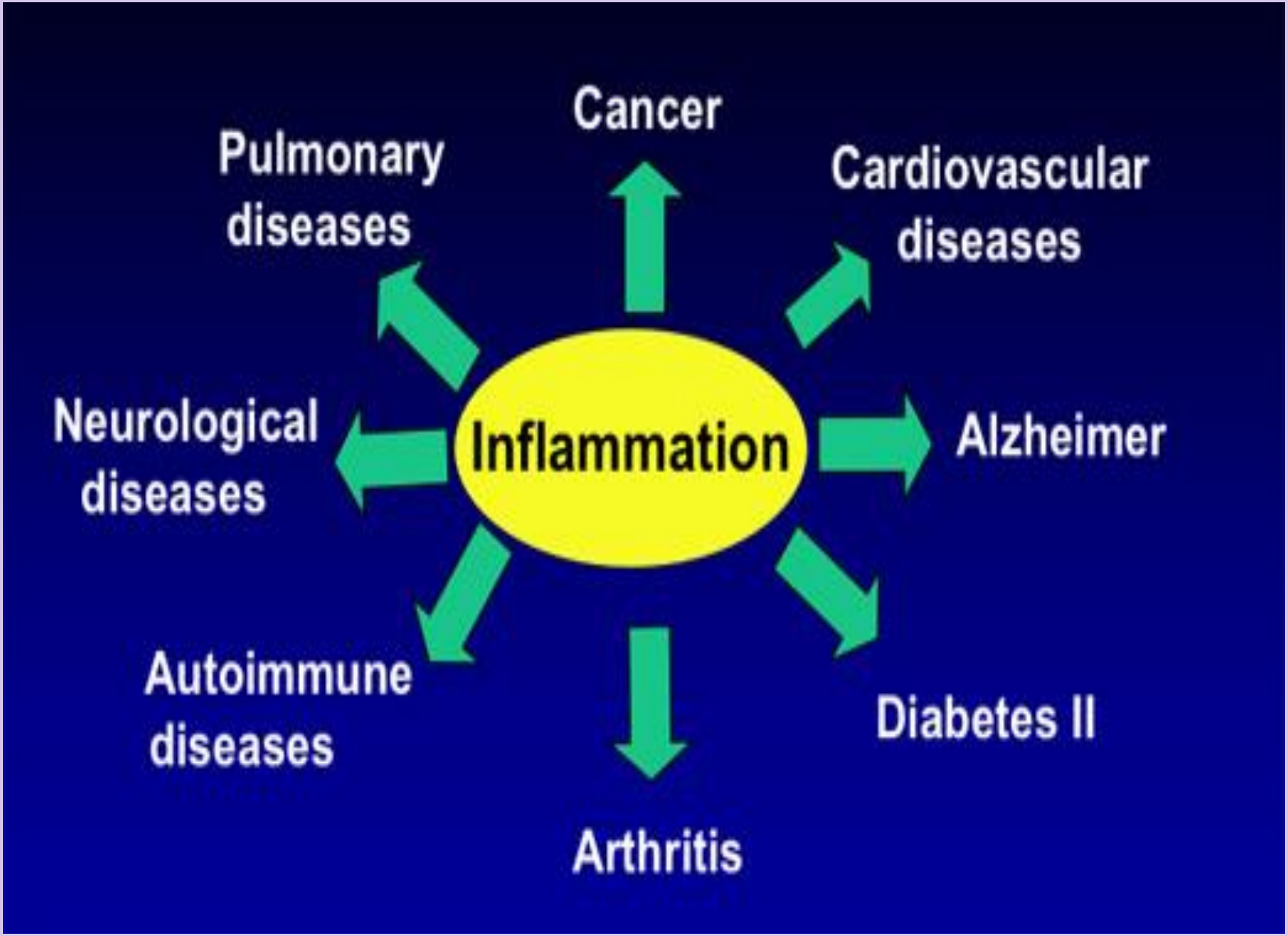
In the pathogenesis of inflammation are three stages: alteration, exudation and proliferation.

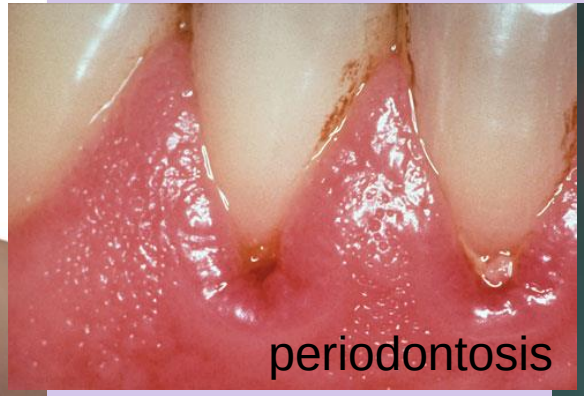


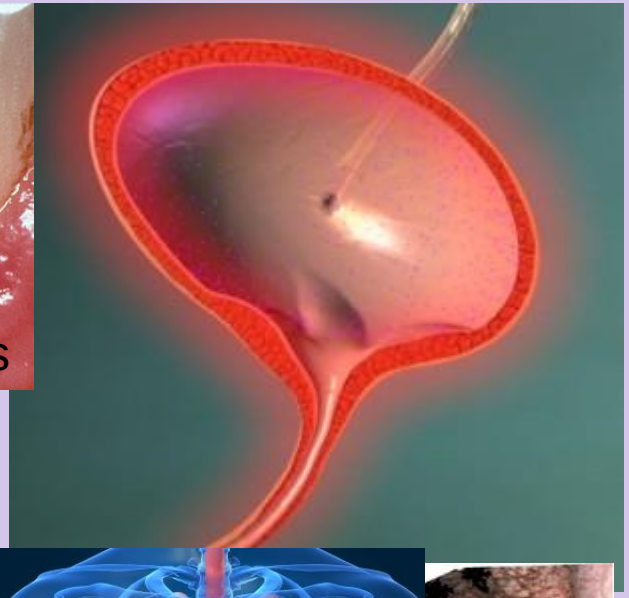
There are 5 symptoms of inflammation:

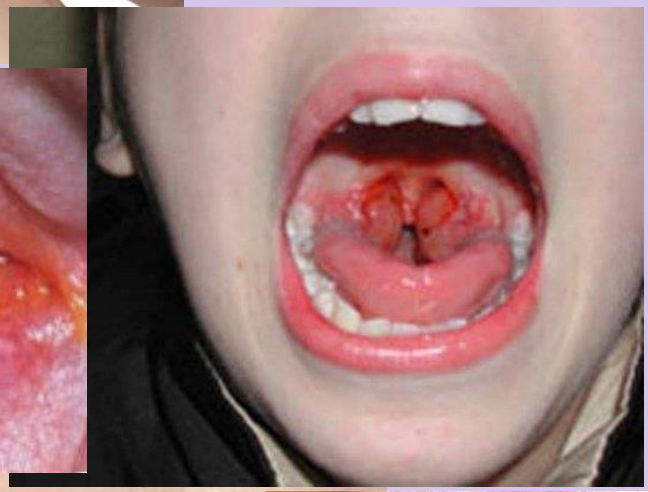
1. **Hyperemia**
2. **Edema**
3. **Pain**
4. **↑ temperature (fever)**
5. **Disorders of motor function**

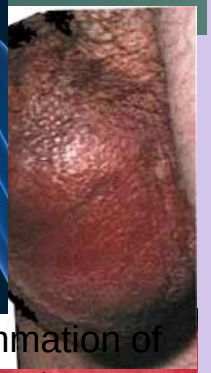



Cancer
Pulmonary diseases
Cardiovascular diseases
Neurological diseases
Inflammation
Alzheimer
Autoimmune diseases
Diabetes II
Arthritis

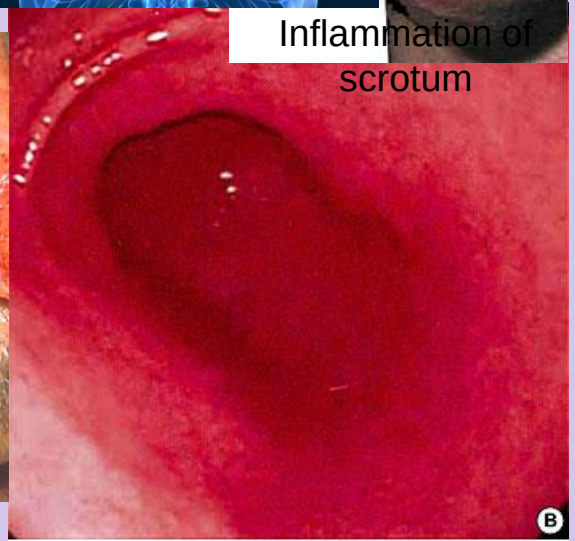


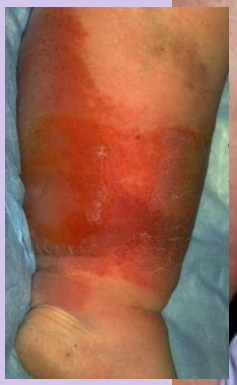


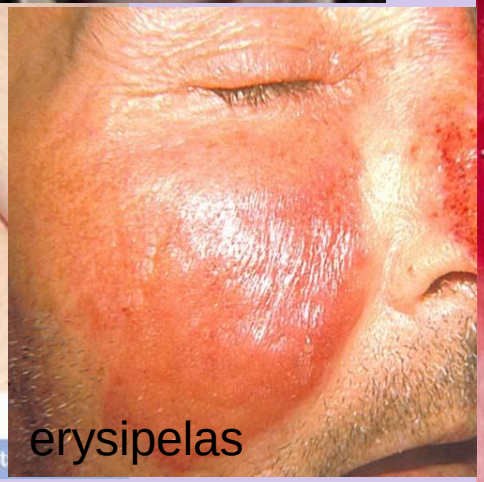




Inflammation of scrotum







Non-opioid analgetics (NOA): non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics-antipyretics (AA)

Synthesis of prostaglandins (PGs) is carried out with the participation of COX (cyclooxygenase): **COX-1** – «physiological» (cytoprotective action in the GIT and kidneys and regulation of the thrombocytes function) and **COX-2** is the «inflammatory» one, which controls the synthesis of PGs during inflammatory processes.

PGs are mediators and modulators of the **inflammation**, **pain** and **fever**: they dilate blood vessels, ↑ the permeability of the vascular wall, that leads to edema develop, hyperemia appears, nociceptors are stimulated (their sensitivity to algogens increases), pyrogenic action on the thermoregulative center.

Characteristics of NSAIDs

- Every seventh patient suffering from rheumatoid diseases takes NSAIDs, and every fifth patient with other pathological conditions that are associated with pain, inflammation and fever administrates these drugs.

- NSAIDs are so popular because they have three main effects: anti-inflammatory, analgesic and antipyretic, which bring relief to patients with relevant symptoms (inflammation, pain, fever). These symptoms occur in many diseases.

- Nowadays there are a large arsenal of NSAIDs (more than 40 chemical substances), and in medical practice are used for treatment more than 1000 drugs based on them.

Classification of NSAIDs

Derivatives of:

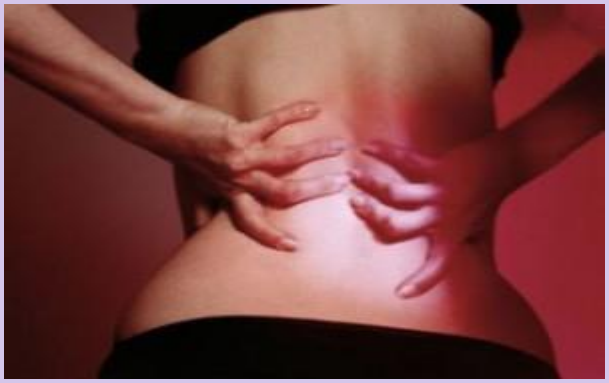
Salicylic acid	Phenylpropionic and phenylacetic* acids	Pyrazolone and indolacetic* acid
Acetylsalicylic acid (ASA) Lysin acetylsalicylate	Ketoprofen Ibuprophen Sodium diclofenac*	Phenylbutazon Clofezone Indomethacin*
Oxycams and fenamates*	**Coxibs**	**Combined and other* medicines**
Meloxicam Piroksikam Niflumic acid* Mefenamic acid*	Celekoxib Rofekoxib	Reopirin Nimesulide* Ketorolac* Sigan

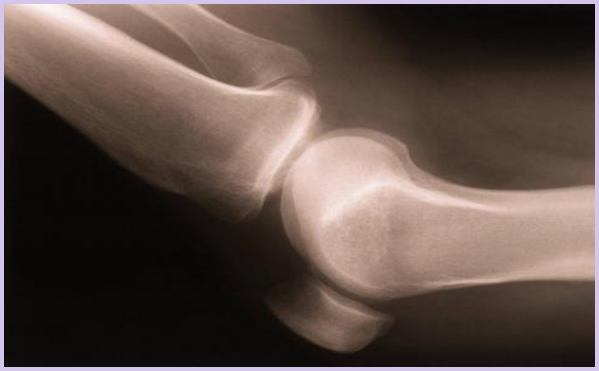
According to the World Health Organization, about 20% of the world population are taking NSAIDs

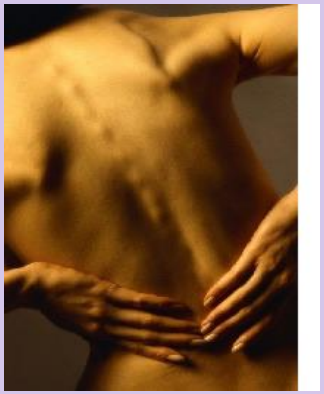
NSAIDs are non-steroidal anti-inflammatory drugs

Pharmacological characteristics of NSAIDs

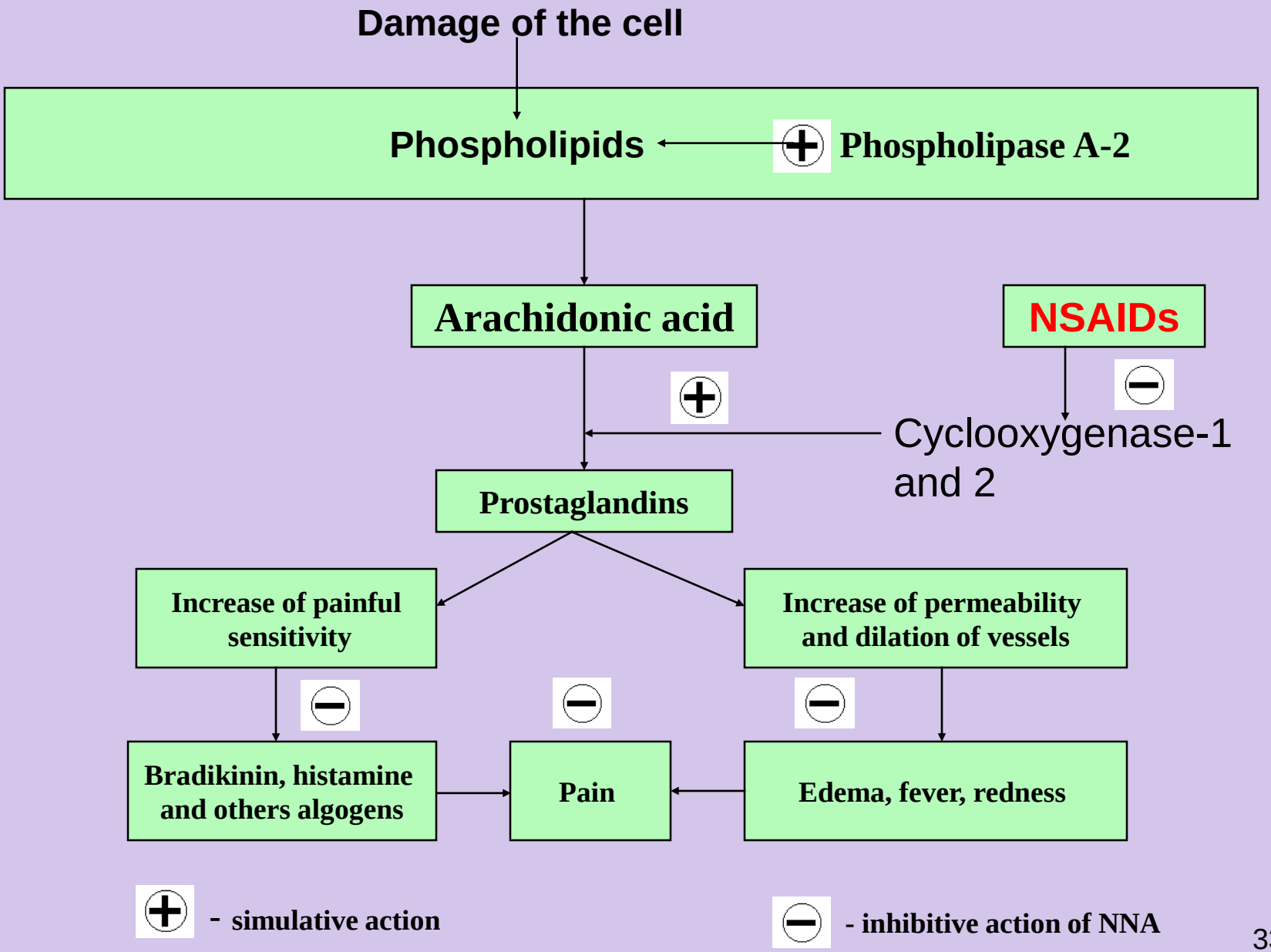
Pharmacodynemics (effects)	Indications
Anti-inflammatory	**Inflammatory diseases of the connective tissue (collagenoses): rheumatism, systemic lupus erythematosus, etc.; arthrites, arthroses, osteochondrosis, radiculitis**
Analgesic	**Acute and chronic pain: headache, pain in joints, muscular pain (myalgia), toothache, algomenorrhea, neuralgia, bruises, etc.**
Antipyretic	**Hyperthermia (fever), ARVI**
Anti-aggregant	**Hypercoagulative syndrome, prophylaxis of postoperative thrombosis, thrombophlebitis, disorder of the cerebral blood circulation, ischemic heart disease, atherosclerosis**







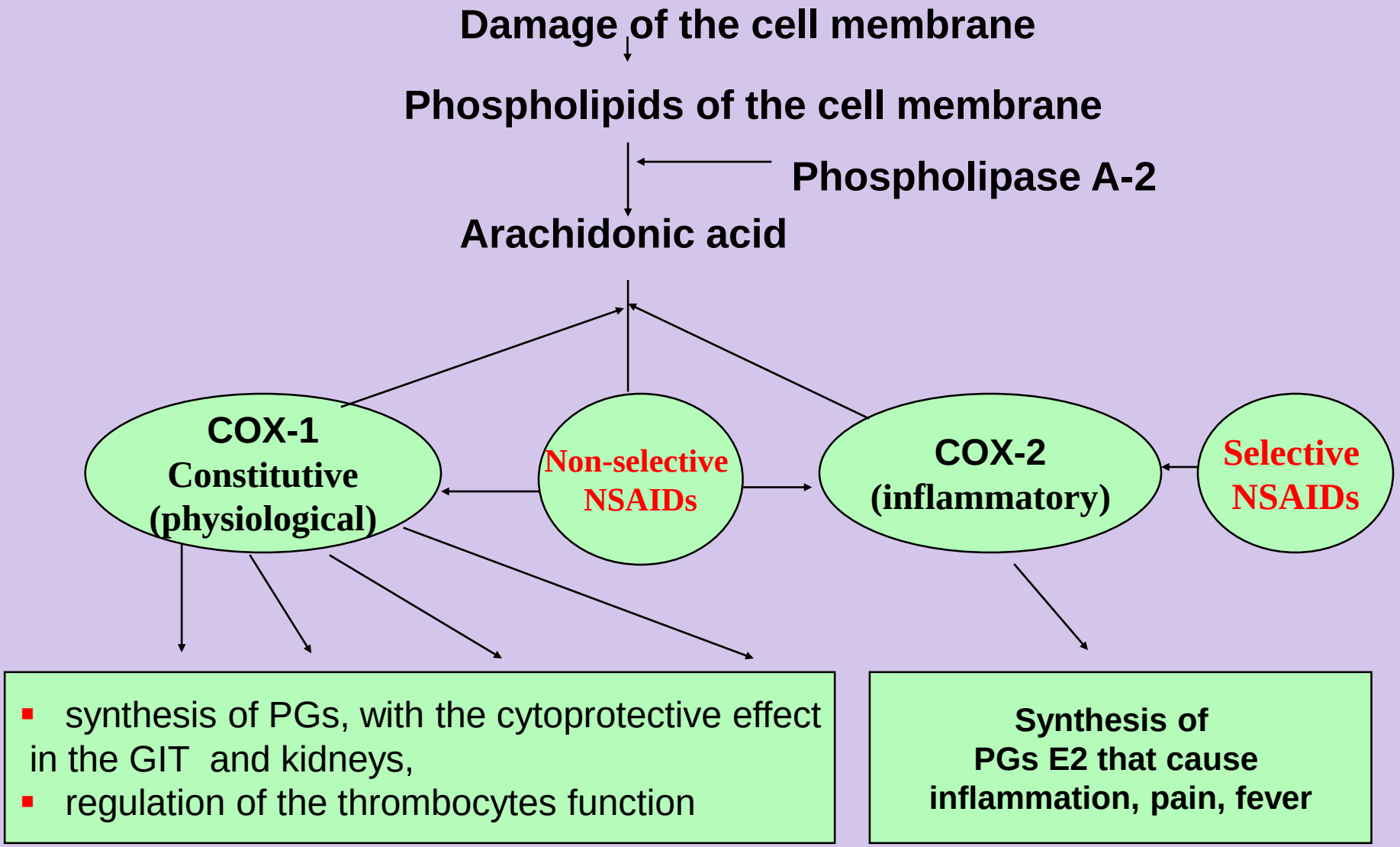
The mechanism of action of NSAIDs



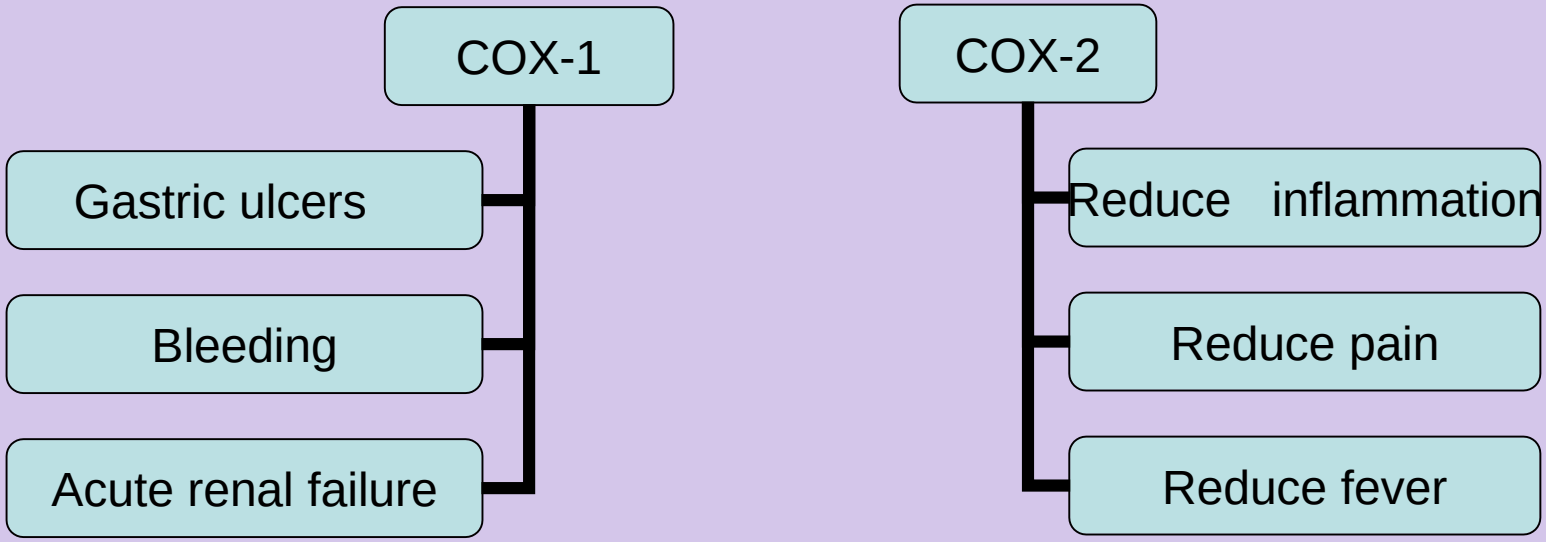
Effects of Prostaglandins

	COX-1: physiological	COX-2: inflammatory
Peripheral injury site		Inflammation
Brain		Increase pain perception Promote fever (hypothalamus)
All organs and tissues in the inflammation state		Disorders of proliferation (reparation)
Stomach	Protect mucous membrane	
Platelets	Increase aggregation of thrombocytes	
Kidney	Vasodilation	

The modern concept of COX



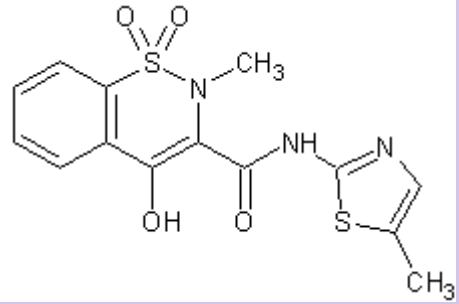
Effects of COX inhibition by most NSAIDs



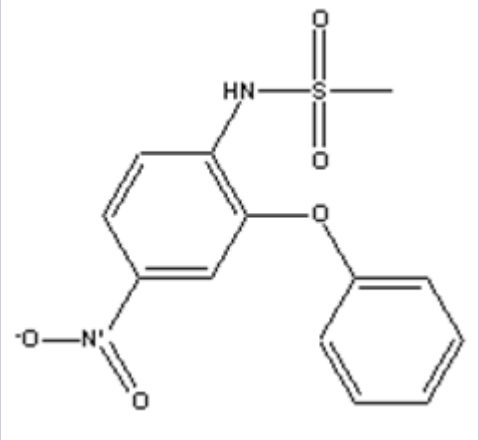
NSAIDs : anti-platelet — decreases ability of platelets to clot

Selective COX-2 inhibitors

Meloxicam



Nimesulide

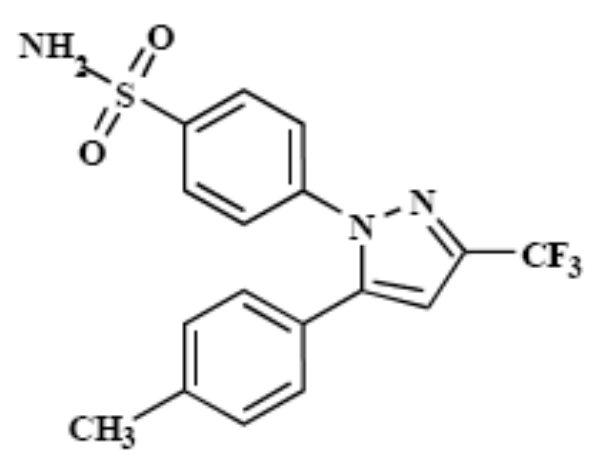


These medicines have higher effectiveness and safety comparing with the other non-selective NSAIDs not only in case of ulcerogenic effect, but renal dysfunction, platelet aggregation, and the negative effect on cartilage. Selectivity decreases with increasing of their dose

Highly selective COX-2 inhibitors

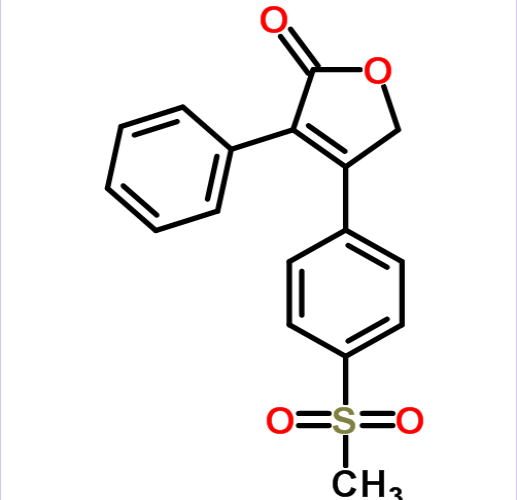
They suppress the activity of the enzyme which is formed in a focus of inflammation (COX-2). They possess anti-inflammatory, analgesic and antipyretic effects. They do not influence platelet aggregation since COX-2 is not synthesized in platelets

Celecoxib



Valdecoxib,
Parecoxib,
Lumiracoxib,
Etoricocoxib

Rofecoxib



Side effects	***Contraindication***
Ulcerogenic effect (especially non-selective COX inhibitors)	Peptic ulcer, gastritis
Allergic reaction	Bronchial asthma, allergic bronchitis
Bleedings	Bleedings, thrombocytopenia, hemophilia
Nephrotoxicity and hepatotoxicity (coxibs)	Renal and liver dysorders
Cardiotoxicity (coxibs)	IHD, hypertension, atherosclerosis

New factors influencing the role of COX-2-dependent PGs synthesis

- both COX enzymes regulate the inflammation reaction development;
- COX-1 is involved in the development of the initial stage of inflammation (60 min.)
- COX-2 modulates the following (after 60 min.) stages of the inflammation;
- COX-2 is present in a healthy body (in the brain and adrenal cortex);
- COX-2-dependent PGs regulate ovulation, kidneys function, cardiovascular system, bone remodeling;
- COX-2 as well as COX-1 play an important role in maintaining homeostasis and restoring the integrity of the gastric mucous membrain

New COX-3 enzyme

(Chandrasekharan N. et al., Proceeding of Academy of Sciences, 2002)

- COX-3 is found in the brain and spinal cord tissues of dogs;
- synthesized in the brain, affects the synthesis of PGsE2 and participates in the development of pain and fever, but unlike other COX enzymes does not have effect on inflammation;
- Inhibition of COX-3 causes central, not peripheral analgesia;
- Selective inhibitor of COX-3 is paracetamol (does not have anti-inflammatory effect).

Classification of analgesics-antipyretics (AA)

With the central component of action	Peripheral-acting *(monomedicines* and combined ones)*	Spasmo-analgesics
Nephopam Paracetamol (paraaminophenol deriv.) Ketorolac (derivative of heteroarylacetic acid)	Sodium methamizole* (Analgin) (pyrazolone derivatives) Pentalgin Tempalgin Citramone Baralgin Sedalgin Citropac	Baralgetas Spazmolgon

Pharmacodynamics (effects) → Indications

Analgesic	**pain that is not dangerous to life (toothache, headache, pain in joints, muscular pain, etc.), neuralgia**
Antipyretic	**Fever, ARVI, flu**

The mechanism of action of AA

- Block of COX leads to inhibition of PGs synthesis (PGs increase sensitivity of nociceptors to chemical and mechanical stimuli) $\rightarrow \downarrow$ sensibilisation of nociceptors to algogens
- The elimination of edema leads to a decrease in pressure on nerve endings
- Antipyretic effect is linked to the suppression of PGs synthesis, leads to a decrease in their pyrogenic effect on the thermoregulative center in the hypothalamus
- An increase in heat loss (skin vessels are dilated, perspiration is increased)

Suppression of prostaglandin synthesis leads to an analgesic effect that is especially prominent in the presence of inflammation

Antipyretic effect of these medicines is present only in case of fever. In normothermia they do not change body temperature

Pharmacological “face" of AA

Medicines	Analgesic	Antipyretic	Anti-inflammatory	Other effect
Sodium metamizol	++ (standard)	+	±	
Paracetamol	+	++	-	?
Ketorolac	+++	±	-	
Tempalgin	+++	+	-	Tranquilizing
Baralgetas	+++	-	-	Spasmolytic
Spasmalgon	++	+	±	Spasmolytic
Sedalgin Pentalgin	+++	+	-	1 aspirin 2 coffeine 3 codeine 4 phenobarbital
Citramon	+++	+	±	1 aspirin 2 coffeine 3 paracetamol

The comparative characteristic of opioid and non-opioid analgetics

Effect	Opioid	Non-opioid
Analgesic effect	Are effective at a severe pain of any origin	Are effective, basically at a pain caused by an inflammation
Antipyretic effect	—	+
Anti-inflammatory effect	—	+
Hypnotic	+	—
Respiratory inhibition	+	—
Euphoria	+	—
Drug dependence	+	—

Pharmacological “face“ of NSAIDs and AA

- **Anti-inflammatory effect**

Sodium diclofenac (D) >Piroksikam (P) ≥ Indomethacin (I) > Meloxicam (M) > Ketoprofen (K) > Fenilbutazon (F) = Ibuprofen (Ib) > Acetilsalicylic acid (ASA)

- **Analgetic effect**

D > I > Metamizol sodium (MS) > P > Ib > Paracetamol (Pa) > K ≥ ASA ≥ F

- **Antipyretic effect**

D > P > I > Ib > Pa > ASA = F

- **Ulcerogenic effect**

I > ASA > F > P > D > Ib

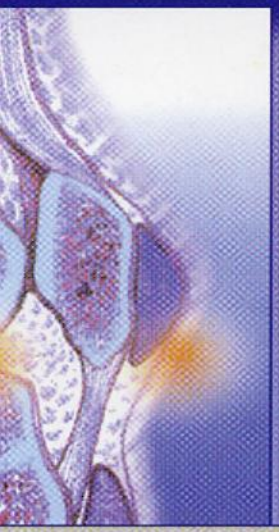
Nowadays the pharmacology of XXI century can provide control over all types of pain.

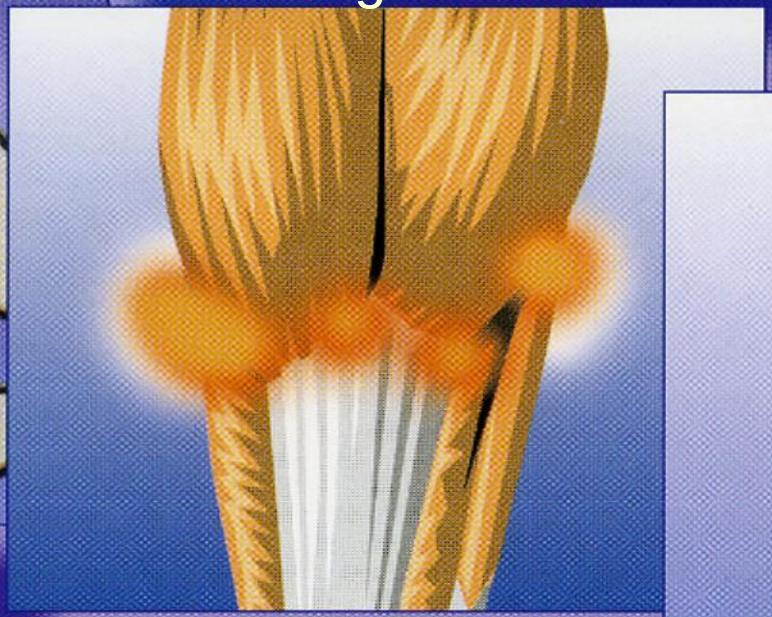
Today, there are more than 200 medicines on arms of doctors and pharmacists that can prevent, reduce and eliminate pain.

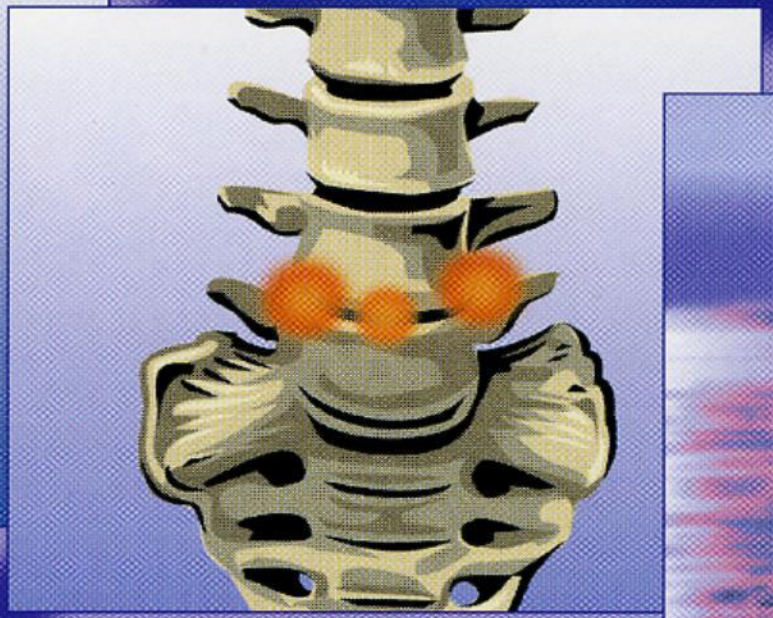
Unsolved questions :

Working out to find an ideal anesthetic:

- Improved safety;
- Overcoming addiction








Thank you