

**ODESSA NATIONAL MEDICAL UNIVERSITY**

**DEPARTMENT OF PHARMACOLOGY AND PHARMACOGNOSY**

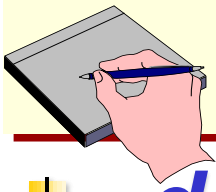
**NON-NARCOTIC**

**AND NARCOTIC**

**ANALGESICS**

# COMPARATIVE CHARACTERISTICS OF ANALGESICS

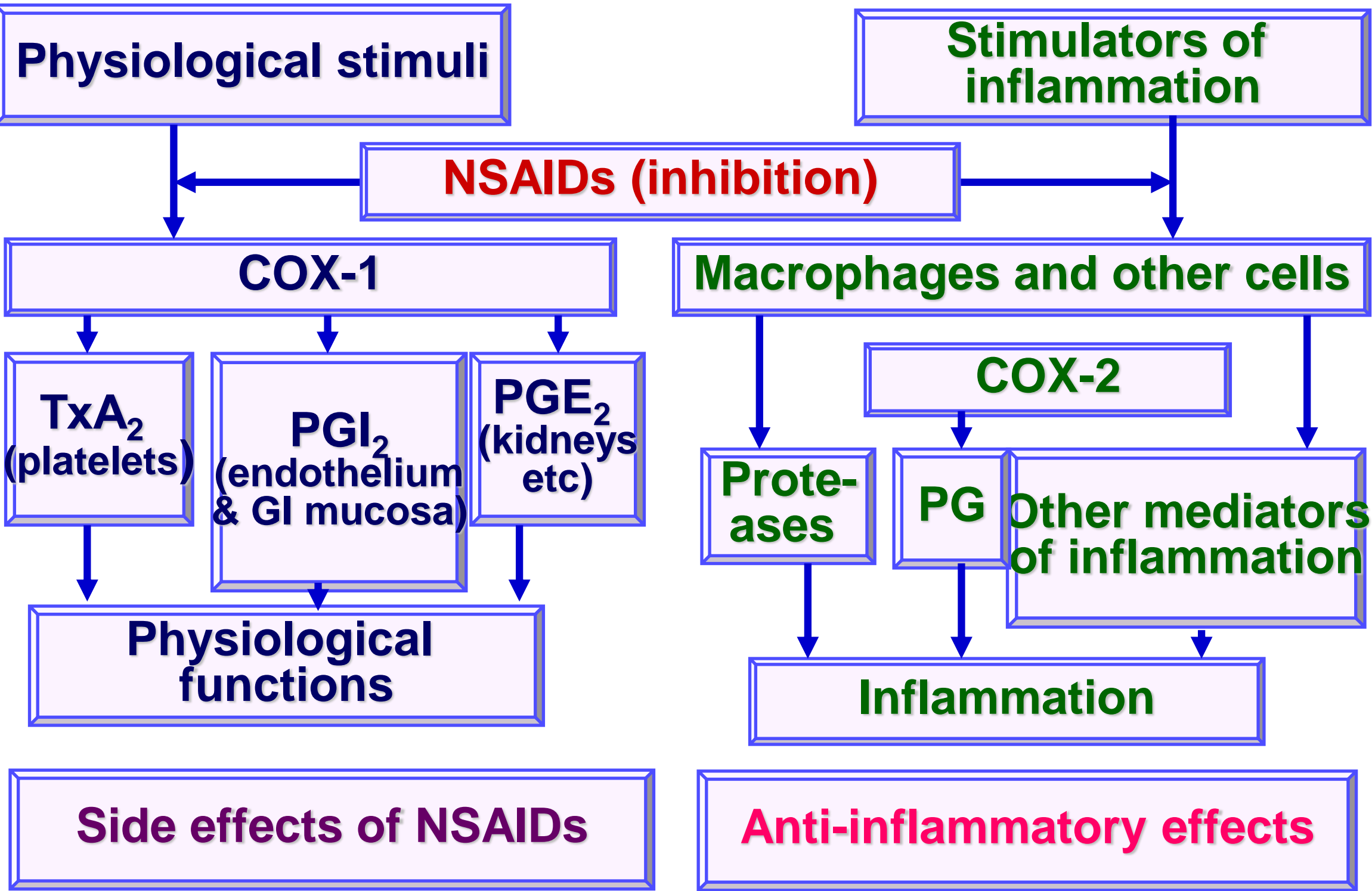
effect	analgesic	
	Narcotic	Non-narcotic
Analgesic	pain of any origin	pain caused by inflammation
Anti-inflammatory	-	+
Anti-fever	-	+
Hypnotic	+	-
Euphoria	+	-
Dependence	+	-
Tolerance	+	-
Breathing depression	+	-



# CLASSIFICATION OF NSAIDs

- + **derivatives of salicylic acid** – acetylsalicylic acid (ASA, aspirin), methylsalicylate
- + **derivatives of pyrazolon** – analgin (metamizole), butadion (phenylbutazone)
- + **derivatives of anylin** - paracetamol (acetaminophen)
- + **derivatives of phenylpropionic, phenylacetic and antranyl acids** – ibuprofen, diclofenac-sodium, ketoprofen, mefenamic acid и др.
- + **derivatives of indolacetic acid** – indomethacin, etodolac
- + **derivatives of oxicams** – pyroxicam, meloxicam
- + **derivatives of different groups** – ketorolac, nimesulid, celecoxib etc.
- + **Combined agents** – baralgin, tempalgin, pentalgin, solpadein etc.

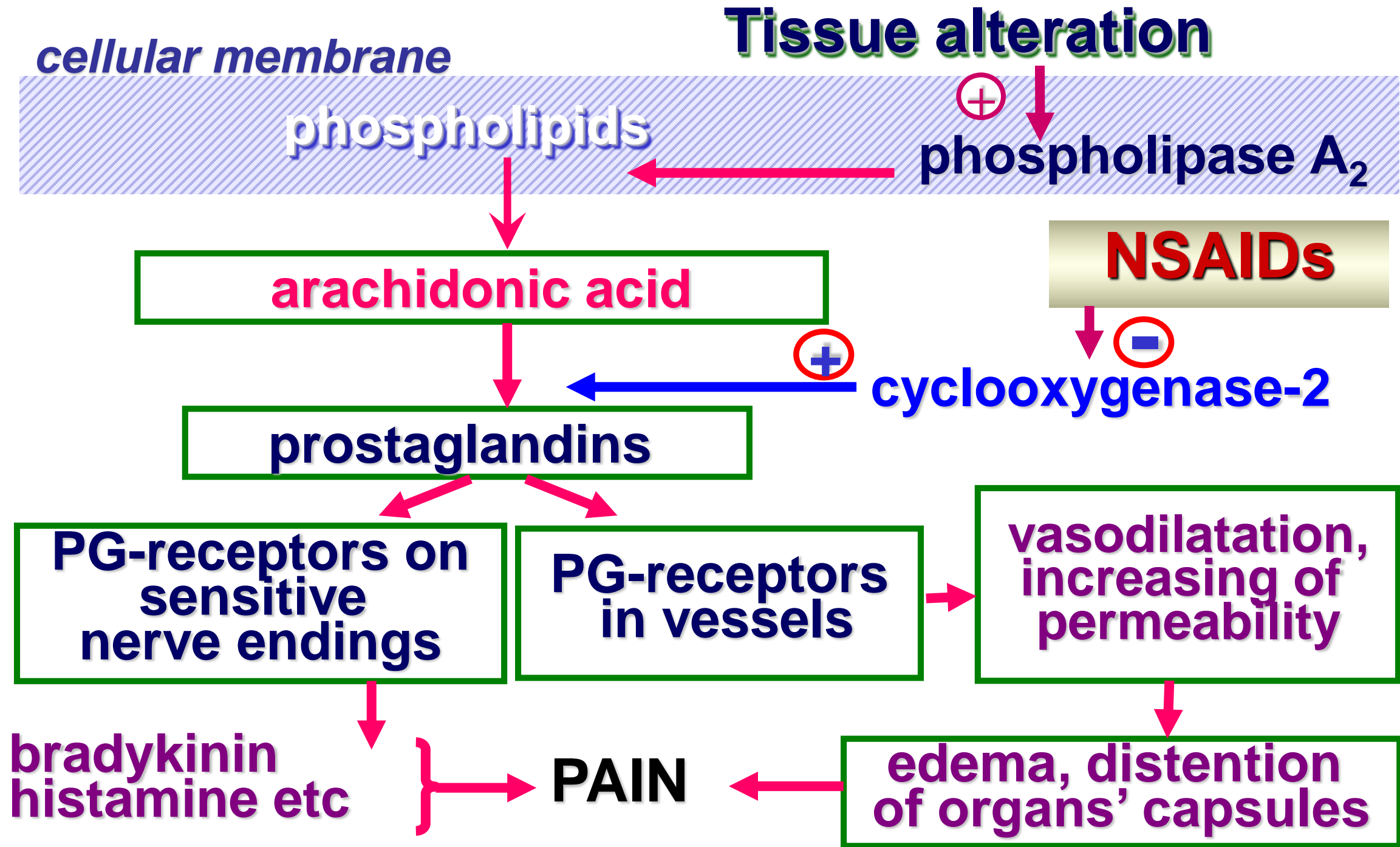
# ACTION OF NSAIDs ON COX-1 & COX-2



# CLASSIFICATION OF NSAIDs ACCORDING TO SELECTIVITY OF CYCLOOXYGENASE INH. (COX-1 & COX-2)

- + inhibitors of COX-1 & COX-2 – *majority of modern NSAIDs*
- + selective inhibitors of COX-1 – *acetylsalicylic acid* (in small doses)
- + selective inhibitors of COX-2 – *nimesulide, meloxicam*
- + highly-active COX-2 inhibitors – *celecoxib*

# MECHANISM OF ANALGESIC ACTION OF NSAIDs





# COMPARISON OF ANALGESIC ACTIVITY OF NSAIDs

**ketorolac > piroxicam > diclofenac  
sodium > naproxen > indomethacin >  
butadion > mefenamic acid > analgin >  
brufen > paracetamol > acetylsalicylic  
acid**

# MECHANISMS OF ANTI-INFLAMMATORY EFFECTS OF NSAIDs

- **Inhibition of prostaglandins synthesis** (inhibition of cyclooxygenase)
- **Inhibition of adhesion** (inhibition of cells migration in site of inflammation)
- **Lysosome** ⇒ ↓ hydrolytic enzymes release (proteases, lipases, phosphatases)
- **Anti-alterative action** (↑ collagen stability and its maturation)
- **Antagonism with mediators of inflammation** (↓ histamine, serotonin, bradykinin synthesis)
- **Decreasing of energy supply of inflammation** (inhibition of ATP synthesis, disintegration of phosphorylation, ATP-ase inhibition)
- **Immunotropic action** (↓ specific reaction on antigen, T-lymphocytes proliferation, interleukin synthesis)



# ANTIPIRYRETIC ACTION OF NSAIDs

*development of fever* →

increasing of **PGE<sub>2</sub>** synthesis in

hypothalamus → deposition of cAMP →

alteration of Na<sup>+</sup> and Ca<sup>2+</sup> ratio →

↑ function of heat center →

↑ thermoproduction → raising of body temperature

**NSAIDs** → decreasing of **PGE<sub>2</sub>** synthesis  
→ restoring of thermoregulatory center  
function → increasing of heat release  
vasodilatation of skin vessels and  
increasing of sweating



# PHARMACOLOGICAL EFFECTS OF MODERN NSAIDS

NSADs	Anti-inflammatory	Analgesic	Antipyretic	Chondro-protective
Meloxicam	100%	100%	100%	100%
Nimesulide	100%	100%	100%	100%
Celecoxib	100%	100%	100%	100%
Ibuprofen	100%	100%	100%	100%
Diclofenac	100%	100%	100%	100%
ASA /aspirin/	100%	100%	100%	100%

# RULES OF NSAIDs PRESCRIPTION

- ✓ **Personal agent's choice:** analgesic effect (first hours) followed by anti-inflammatory (after 10-14 days of regular usage)
- ✓ **Dosing** (up- and down- methods)
- ✓ **Time of ingestion:**
  - after meal; for achievement of rapid analgesic or antipyretic effect should be given 30 min before meal or 2 hrs after meal with 1/2-1 glass of water; after ingestion it is recommended not to lie for esophagitis prevention
  - according to time of maximal disturbances: at morning stiffness it is wise to take a quickly absorbed drug in the morning (naproxen, diclofenac-sodium, aspirin-upsa, ketoprofen) or prescribing of long-acting agents at bedtime

# THERAPEUTIC USES OF NSAIDs

- **after-operation pain** of intermediate intensity
- **headache, toothache**
- **spasms of bile-, urinary ducts** (in combination with spasmolytics)
- **connective tissue diseases** (rheumatoid arthritis, osteoarthritis, back pain, myocarditis, glomerulonephritis etc.), **gout** (indomethacin, naproxen etc)
- **traumas, inflammations** (injures, joint dislocation, miositis, neuralgia etc)
- **fever** during infectious diseases
- **Prevention and treatment of thrombosis – ASA**  
(325 mg once in 3 days)



# PHARMACOKINETICS OF NSAIDs

**Absorption:** majority – **weak acids** ⇒ absorption **in stomach**; if **↑ pH** upto 3,5 **↓** ulcerogenic effect but effectiveness as well;

**Administration:** oral, rectal, I.M., I.V., transdermal; possible **first-pass effect!**

**Plasma protein binding:** **50-99 %**, ASA replace  $T_3$ ,  $T_4$ , uric acid, phenytoin, oral anticoagulants

**Distribution:** well-penetrate, including BBB (especially at acidosis) !

**Biotransformation:** significant amount of ASA conjugate with glucuronic acid, glycin, undergo oxidation to non-active metabolites; certain are excreted unchanged (**ketorolac**)

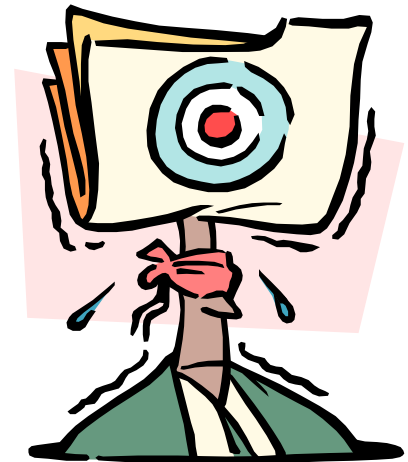
**Excretion:** mainly, via kidneys, urine alkalinization **↑ excretion**.  $T_{1/2}$  ASA in daily dose 0,6 g – **4-5 hrs**, in dose 4 g – **upto 15 hrs!**

# ULCEROGENIC ACTION OF NSAIDs

- dyspepsia – 30-40 %
- gastric and duodenal erosion or ulcer – 10-20 %
- bleeding and perforation – 2-5 %

**Ulcerogenic risk:**

ketoprofen > piroxicam > indomethacin >  
naproxen > aspirin > diclofenac > analgin >  
ibuprofen



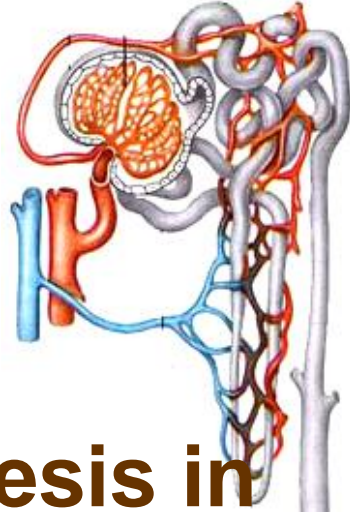
# ULCEROGENIC EFFECTS OF NSAIDs

## improvement of drugs' tolerance:

- ✓ Simultaneous administration of drugs that protect GI mucosa: NSAID + misoprostol, proton pump inhibitors, H<sub>2</sub>-antagonists (?), cytoprotectors (sucralfate)
- ✓ Changes in treatment strategy: dosage decreasing; shift for parenteral (?), rectal (?) or local application; usage of intestinal-dissolved drugs; usage of pro-drugs (sulindac)
- ✓ Usage of selective COX-2 inhibitors (meloxicam, nimesulide, celecoxib)

# NSAIDs NEPHROTOXICITY

(5-10 %):



## ➤ Renal failure:

- blockage of  $\text{PG-E}_2$  and prostacyclin synthesis in kidneys  $\Rightarrow$  vasoconstriction and  $\downarrow$  renal bloodflow  $\Rightarrow$   $\downarrow$  GFR and diuresis
- $\Rightarrow$  disturbance of water-salt balance: water, sodium retention, hypercreatinemia, edema,  $\uparrow$  ABP (indomethacin, butadion, COX-2 inhibitors)

## ➤ Direct action on renal parenchyma:

- acute papillary necrosis (ibuprofen)
- acute interstitial nephritis – «analgesics nephropathy» (butadion, indomethacin, analgin, ibuprofen, paracetamol)



# NSAIDs HEPATOXICITY

<b>Agents</b>	<b>Type of injury</b>	<b>Mechanism of injury</b>	<b>Relative frequency</b>	<b>Mortality</b>
<b>Aspirin</b>	hepato-cellular	toxic	dose-dependent	Yes
<b>Butadion</b>	-»-, cholestasis	-»-, hyper-sensitivity	3	Yes
<b>Indome-thacin</b>	hepato-cellular	unknown	2	Yes
<b>Ibuprofen</b>	-»-	-»-	1	Yes
<b>Ketoprofen</b>	enzymes turnover	-»-	1	No
<b>Piroxicam</b>	hepato-cellular	hyper-sensitivity	1	Yes
<b>Diclofenac</b>	-»-	unknown	3	Yes

**Paracetamol – direct toxin (at daily dose > 6 g)**

**Selective COX-2 inhibitors are also hepatotoxic**

# Dyscrasia cause by NSAIDs

- **anemias** (hypochromic anemia, hemolytic anemia etc) – **pyrazolons, indomethacin, ASA**
- **thrombocytopenia** (cytotoxic reaction of allergic origin)
- **leucopenia upto agranulocytosis** – **pyrazolons**
- **coagulopathy with bleeding**: ↓ platelets aggregation (антиагрегантное) and prothrombin synthesis in liver (mild anticoagulant) – **ASA, indomethacin**
- **methemoglobinemia** – **paracetamol**
- **acute intravascular hemolysis with following renal failure** (deficiency of glucose-6-phosphate dehydrogenase) – **ASA**

# OTHER ADVERSE EFFECTS OF NSAIDs

- **CNS:** headache, dizziness, fatigue, insomnia, mental confusion (ASA, ketorolac, indomethacin etc – 1- 10 %)
- **allergic reactions (12-15 %):**
  - angioedema, allergic interstitial nephritis, Steven-Johnson, anaphylaxia (especially pyrazolon derivatives)
  - «aspirin asthma», rhinitis, conjunctivitis – ASA
  - alopecia – brufen
  - frequency of appearance: diclofenac > piroxicam > brufen > indomethacin > ketoprofen

# OTHER ADVERSE EFFECTS OF NSAIDs

- **cardiovascular toxicity:** ↑ BP, heart beat – celecoxib, myocardiodystrophy – butadion
- **cartilage tissue degeneration**
- **teratogenic** (ASA – palatine dissection in fetus (8-14 per 100 observations); **fetotoxicity** (indomethacin – preterm closing of ductus arteriosum); **prolongation of pregnancy and delivery** (indomethacin etc)
- **mutagenic effect** (↑ chromosomal abberation in lymphocytes – ASA, butadion)
- **Rey's syndrome in children** (heave hepatic encephalopathy with mortality ↑ 50%)

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# NARCOTIC ANALGESICS

**Agents that are able at resorptive action *nto* suppress pain impulses transmission, *aat* repetitive uses able to produce physical dependence (drug-abuse)**

## Sources:

**opium (from Greece. *opos* - juice) – dry poppy juice (Papaver somniferum)**

## Opium alkaloids:

- **fenantrane derivatives: *morphine, codeine, tebaine***
- **isoquinolone derivative: *papaverine, narcotin***



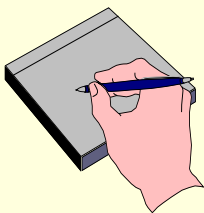


***Alkaline-like plant-origin compounds that contain nitrous***

- **solid, colorless, bitter, optically active**
- **alkalines are bases that are badly dissolved in water, well – in organic solvents**
- **salts of alkaloids – visa versa**

## ***Inactivation reactions***

- **Tanin, iodides →**
- **Potassium permanganate → universal oxidizer**



# CLASSIFICATION OF NARCOTIC ANALGESICS ACCORDING TO CHEMICAL STRUCTURE

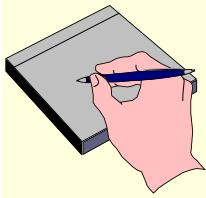
- **derivatives of fenantren:**
  - **opium alkaloids** – *morphine, codeine, omnopon*
  - **synthetic analogues** – *ethylmorphine, buprenorphine, nalbuphine, nalorphine, naloxone, naltrexone*
- **derivatives of benzomorphans** – *pentazocine*
- **derivatives of piperidine** – *promedol (trimeperidine), fentanyl, looperamide*
- **derivatives of heptanone** – *methadone*
- **different chemical groups** – *tramadol etc*



# FUNCTION OF OPIOID RECEPTORS

Opioid receptors ( $\mu$ ,  $\kappa$ ,  $\delta$ ,  $\epsilon$ ,  $\sigma$ ) – lipoprotein sites with high affinity to endogenous peptides (enkephalines, endomorphines) and narcotic analgesics in neuronal membranes that transmit pain impulses

properties	$\mu$ (mu)	$\kappa$ (kapa)	$\delta$ (delta)
<b>Activation</b>	analgesia, dependence, euphoria, vegetative reactions	analgesia, sedation, miosis	emotion, seizures, vegetative reactions
<b>Activators:</b> • endogenous peptides • narcotic analgesics	$\beta$ -endorphines MET-enkephalines morphine, fentanyl, promedol etc	dinorphine neoendorphine  pentazocine, buprenorphine etc	leu-enkephaline  -



# CLASSIFICATION ACCORDING TO AFFINITY TO OPIOID RECEPTORS

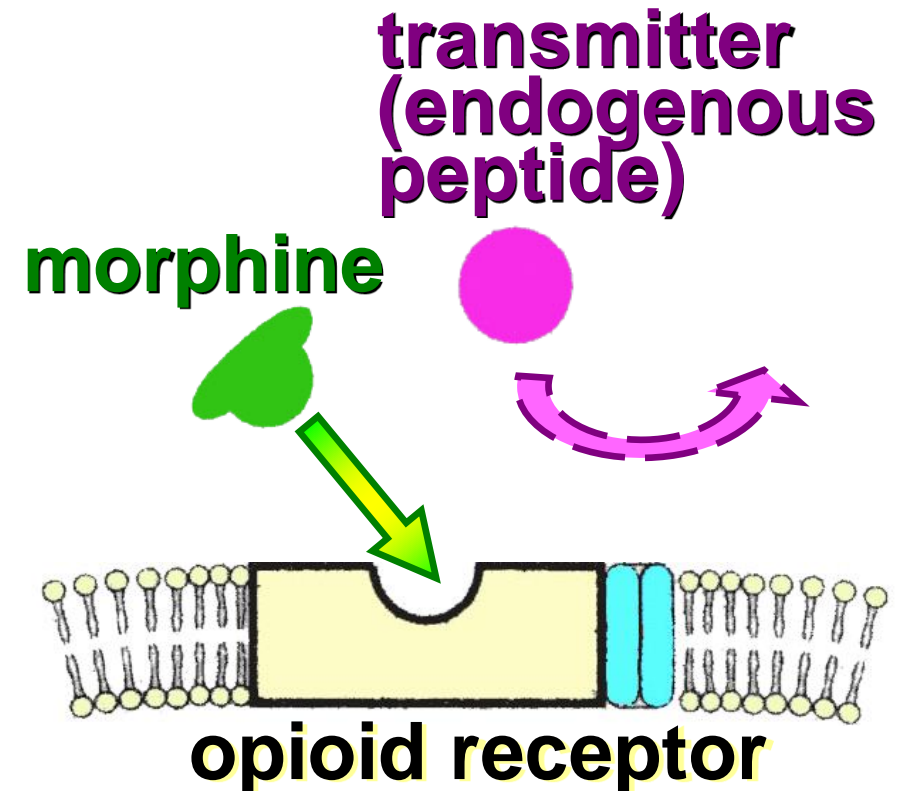
## ● Agonists:

- Strong (full) – *morphine, promedol, fentanyl, methadone*
- Moderate – *codeine, omnopone*

## ● Agonists-antagonists:

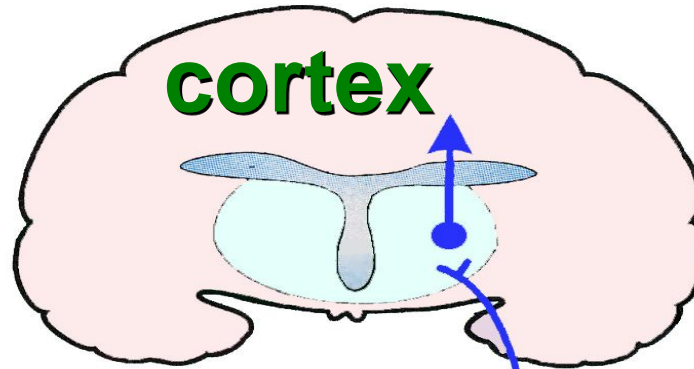
*buprenorphine, nalorphine, pentazocine, tramadol*

## ● Antagonists: *naloxone, naltrexone*



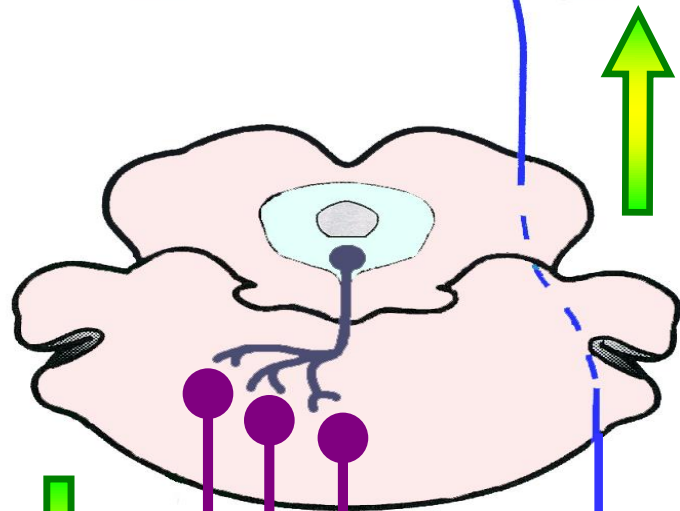
# SITES OF MORPHINE'S ACTION

III level



intermediate  
brain (thalamus)

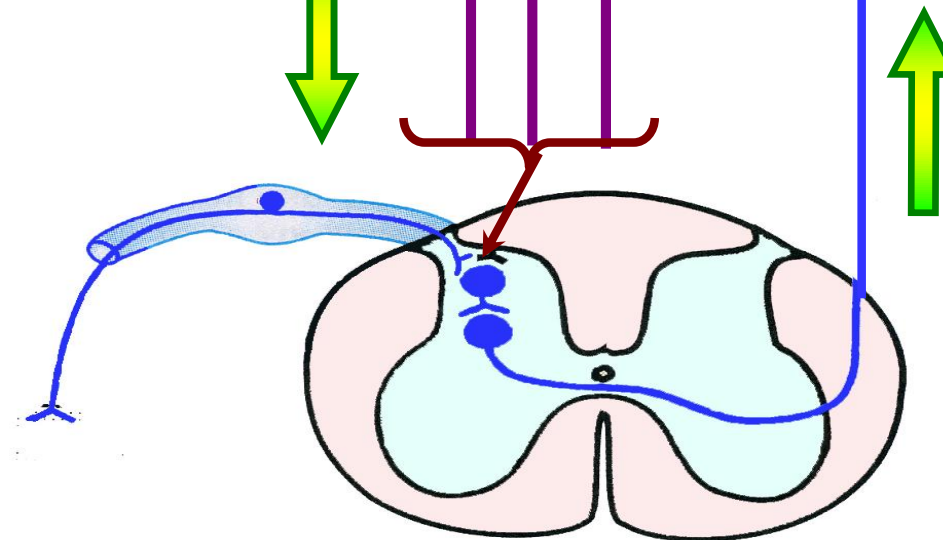
II level



middle brain  
(central grey matter)

medulla  
oblongata (raphes  
nuclei)

I level



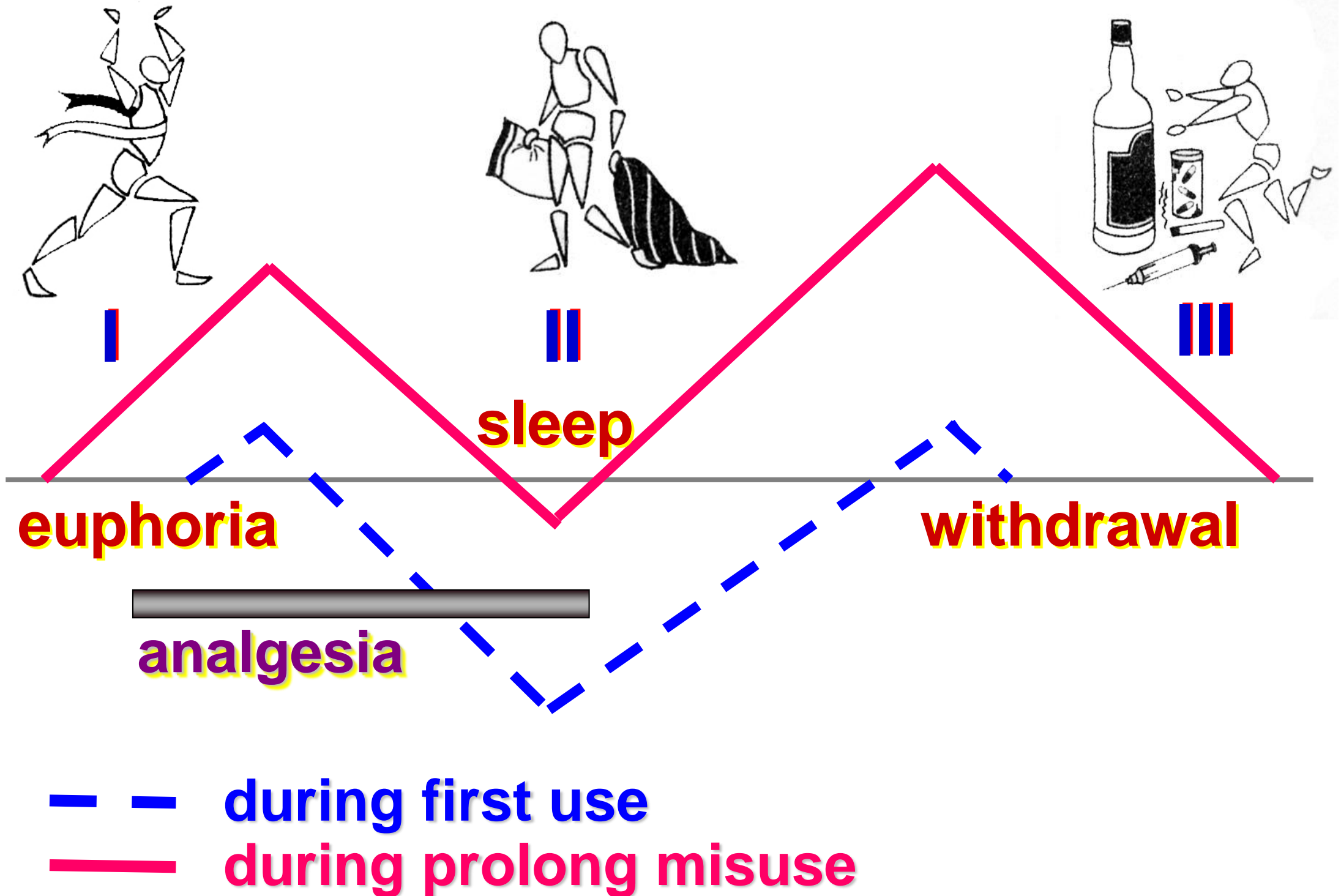
posterior horns  
of spinal cord

alteration

# ANALGESIC ACTION OF NARCOTIC ANALGESICS

- ✚ insignificant increasing of pain threshold
- ✚ inhibition of pain transmission in spinal cord
- ✚ presence of anti-anxiety and euphoric effects, suppression of pain expectation etc
- ✚ mainly effective during chronic visceral pain  
висцеральных болях

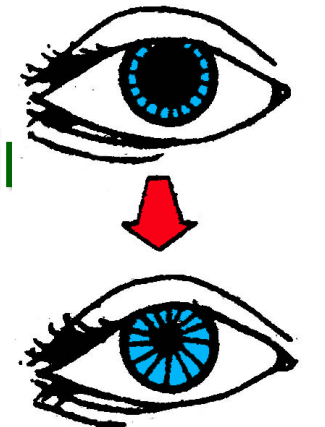
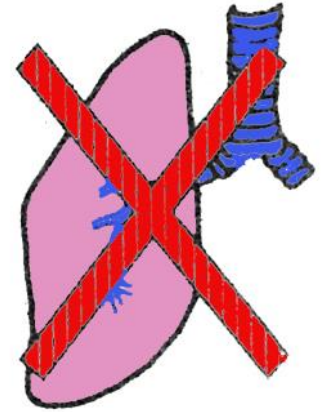
# STAGES OF MORPHINE ACTION



# MORPHINE PHARMACODYNAMIC

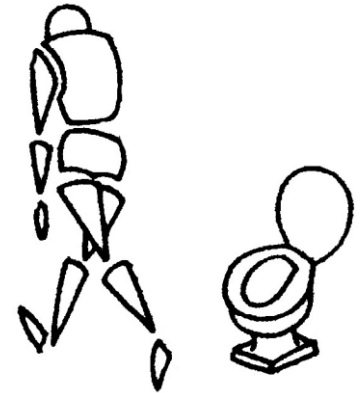
## CNS:

- ✚ **Brain cortex:** euphoria (“rush”), sedation, shallow sleep
- ✚ **Medulla oblongata:**
  - **respiratory center** – ↓ (decreasing of frequency and amplitude of breathing excursion, decreasing of CO<sub>2</sub> sensitivity)
  - **cough center** – ↓
  - **heat center** – ↓ (hypothermia)
  - **n. vagus center** – ↑ (bradycardia, bronchospasm etc)
  - **vomiting center** – ↑ or ↓
- ✚ **Middle brain:** ↑ center of III cranial nerve pair (miosis)
- ✚ **Spinal cord:** ↑ spinal tendon reflexes



# MORPHINE PHARMACODYNAMIC

- **CVS:** insignificant dropping of BP, bradycardia, increasing of intracranial pressure
- **breathing:** bronchospasm
- **GIT:** ↑ tonus, spasm of gastric, intestinal, Oddi's sphincters, but ↓ peristaltic ⇒ prolong evacuation of meal from stomach (8-12 hrs), constipation and spasmogenic effects (colics)
- **urinary bladder:** ↓ urination (sphincters' spasm, ↑ secretion of ADH), but ↑ tonus ⇒ colic; **uterus:** ↓ tonus



# PHARMACOKINETICS OF NARCOTIC ANALGESICS

**Administration:** the majority are well-absorbed from oral, nasal, GI mucosa

**Bioavailability:** undergo first-pass effect  $\Rightarrow$  S.C., I.M., I.V., transdermal (fentanyl), oral (codeine);

**Plasma-protein binding:** 20-96 %

**Distribution:** initially well penetrate into CNS, lungs, liver, kidneys, spleen; later – into skeletal muscles (reservoir), fat tissues

**Biotransformation:** significant part metabolized in polar non-active compounds, esters (heroin), hydrolyzed to morphine; part conjugated with glucuronic acid (morphine etc).

**Excretion:** via kidneys, partially with bile  
T  $\frac{1}{2}$  of morphine – 4-6 hrs!



# COMPARATIVE CHARACTERISTICS OF NARCOTIC ANALGESICS

<b>indicators</b>	<b>morphi ne</b>	<b>prome dol</b>	<b>fenta- nyl</b>	<b>penta- zocine</b>	<b>trama- dol</b>
<b>dose (mg)</b>	<b>10</b>	<b>20-40</b>	<b>0,1</b>	<b>30</b>	<b>50-100</b>
<b>duration of action (hrs)</b>	<b>4-5</b>	<b>3-4</b>	<b>0,5</b>	<b>2-3</b>	<b>3-5</b>
<b>euphoria</b>	<b>+++</b>	<b>++</b>	<b>+</b>	<b>+</b>	<b>+</b>
<b>respiratory depression</b>	<b>+++</b>	<b>++</b>	<b>++++</b>	<b>+</b>	<b>+</b>
<b>hemodynamic</b>	<b>↓ HR</b>	<b>Uncha nged</b>	<b>↓ BP, ↓ HR</b>	<b>↑ BP, ↑ HR</b>	<b>↓ BP, ↑ HR</b>
<b>spasmodic effect</b>	<b>+++</b>	<b>++</b>	<b>+++</b>	<b>+</b>	<b>+</b>
<b>nausea, vomiting %</b>	<b>35-40</b>	<b>2-35</b>	<b>Rarely</b>	<b>2-6</b>	<b>5</b>
<b>withdrawal</b>	<b>+++</b>	<b>+++</b>	<b>++</b>	<b>++</b>	<b>+</b>

# THERAPEUTIC USES OF NARCOTIC ANALGESICS

- **Serious traumas and burns** (morphine, promedol, fentanyl etc.)
- **Myocardial infarction** (fentanyl etc.)
- **Pulmonary edema** (morphine, promedol)
- **Renal and liver colics, acute pancreatitis** (pentazocine, promedol, fentanyl, omnopone etc)
- **Uncurable cancer** (morphine, promedol etc)
- **Preanesthetic medication & postoperative period** (pentazocine, morphine, promedol, fentanyl)
- **Neuroleptanalgesia, ataralgesia** (fentanyl)
- **Spinal analgesia** (morphine)
- **Pain relieve during delivery** (pentazocine, promedol)

# ADVERSE EFFECTS OF NARCOTIC ANALGESICS

- **restlessness, tremor, hyperactivity (if dysphoria)**
- **respiratory depression**
- **nausea, vomiting, constipation, urine retention**
- **postural hypotension (if hypovolemia),  
↑ intracranial pressure,**
- **Itching, angioedema (after parenteral administration)**
- **tolerance, including cross-resistance: begins after 1<sup>st</sup> dose; more quickly develop for analgesic, euphoric, respiratory depression, later - to hypotensive, vomiting, antidiuretic effects; but not to myorelaxant, constipative, convulsive**
- **psychical and physical dependence – drug-abuse**

# ABUSE – CHRONIC POISONING

- **psychical dependence:** euphoria, emotional indifference lead to abuse;
- **physical dependence:** accompanied with tolerance; the main goal – to avoid withdrawal syndrome
- **withdrawal syndrome:**
  1. **acute phase (7-10 days):**
    - ✓ after 8-10 hrs – lacrimation, yawning, rhinorhea, sweating
    - ✓ after 36-48 ч – insomnia, tiredness, rigor, «goose» skin, nausea, vomiting, myalgia, uncontrolled movements, dyspnea, fever, hypertension, diarrhea
  2. **protracted phase (26-30 weeks) – hypotension, bradycardia, hypothermia, mydriasis, ↓ respiration**
- **during disease progression:** alteration of psychical activity (irritability, flaccidity, decreasing of self-estimation), loss of appetite, of skin sensitivity, sweating and other vegetative disturbances

# ACUTE POISONING BY NARCOTIC ANALGESICS

- mental confusion, coma
- miosis, followed by mydriasis
- hypothermia
- hypotension
- breathing is rare (2-4 per min), that can turn to Chein-Stoke
- urine retention
- preserving of spinal tendal reflexes (unlike barbiturates !)
- acidosis



*Opium-user, 1872  
V. Vereschagin*

**The reason of death – respiratory center depression !**

# FIRST AID AT POISONING BY NARCOTIC ANALGESICS

- **Breathing restoration (mechanical ventilation)**
- **Antidote therapy**
  - **Physiological antagonists:**
    - ✓ competitive – **naloxone (0,001-0,004 I.V.)**
    - ✓ non-competitive – **atropine**
  - **Physical – adsorbents**
  - **Chemical – potassium permanganate**
  - **Stomach lavage**
  - **Speeding up of drugs' excretion (hydration & dehydration therapy)**
  - **Hemosorption**
- **Symptomatic therapy:**
  - **Myotroic anti-spasmodic**
  - **Alkaline solution**
  - **cardiotonic**
  - **Catheterization of urinary bladder**

